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THE AMERICAN ACADEMY OF PEDIATRICS' PLACE IN AMERICAN MEDICINE

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IT SEEMS timely to attempt a discussion of the Academy's place in American medicine—its place as an organized group in relation to government and state agencies interested in the area of child health and its place in the lower echelons. The purpose of any such discussion should be to define our area more accurately in order to cooperate with other groups most effectively with minimum overlapping of activities. The American Academy of Pediatrics has now grown up into a mature organization and must take its place as an authority—as a leader in the field of public health in its broad sense.

The ideas that may be expressed in this discussion are by no means original for I have borrowed freely from experiences with our Academy Study, from a close association with the follow-up committee of the Study, known as the ICH Committee, and from my many friends in the Academy over the country. It is hardly necessary to add that I have had the privilege of reading the history of the Academy by our historian, Dr. Marshall C. Pease, and may unconsciously express his comments as if they had been coined by me.

In the first place, the Academy must be the authority in the practical side of child care, especially as it has its application to child health. We must have the "know how." My thought is not difficult to illustrate. The Study of Child Health Services,[1] recently completed, puts the Academy in a position of authority in the area of distribution of medical care for children. Not only do we know some figures but we are aware of their limitations and interpretation. We also realize that to maintain our position of authority, we must keep our knowledge up-to-date by continuing study and take prompt action to remedy the deficiencies which we know exist.

Again there are most important committee studies both of the past and more recently which have made us authorities in specific, more limited areas of child health. I refer with great pride to the work which some of us started a number of years ago in the field of the newborn and more specifically the premature infant. The Academy, through the offices of its Committee on the Fetus and Newborn, has compiled a résumé of the

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best practices for the care of these infants. We are looked upon, therefore, as a group with members who are the leaders in this area.

One could extend this theme further, emphasizing the fact that the Academy first and foremost must be and is interested in clinical pediatrics—how to promote the health of children in every possible way. This meeting is evidence of this great interest and desire to be among those who can give children the benefits of most recent advancements in medical care. With the privilege of attending meetings such as this where there is an exchange of medical ideas and experiences, there comes a responsibility or, better, an opportunity, to serve the general public as well as our individual patients. Because we made the Study, because we were instrumental in promoting better care for the newborn, the Academy must in some way establish permanent and continuous leadership in these and allied fields.

It is of great historical interest that for the past half century pediatricians have always displayed a peculiar interest in preventive medicine and public health. If one reviews the various groups antedating the formation of the Academy, there was always a group of pediatricians in the vanguard trying not only to reduce the mortality of the babies under their care but working out plans nationally, in states and locally to reduce infant mortality. We are now reaping the fruits of their labors.

It was not until about 20 years ago when our Academy was formed that we had an organization that represented the rank and file of all the pediatricians in this country. Here we find the same objective and interest in the public health as the only logical way to promote private health. Article III, Section 1, of our constitution reads, "To maintain the dignity and efficiency of pediatric practice in its relationship to public welfare." It is hardly necessary to remind you that the actual incident that spearheaded the formation of the Academy concerned a public health act. I quote from the unpublished tome of the Academy history by Marshall Pease:[2] "The Sheppard-Towner Act, a modest maternal and infant program, had recently been introduced into Congress and was brought before the (pediatric) section (of the American Medical Association) for serious consideration. The discussion finally ended with a resolution approving the act on the same day the House of Delegates of the American Medical Association passed a resolution condemning the Sheppard-Towner Act. On the following morning the St. Louis papers appeared with banner headlines, quoting the resolution in support of the Sheppard-Towner Act as passed by the Pediatric Section of the American Medical Association. Appended at the end of their article in fine print was inserted the unfavorable resolution of the House of Delegates of the American Medical Association." This is not the place to discuss the tact or courage of our pediatric founders but the above incident shows so clearly that the interest and motivation were the same then as now among those interested in child health.

The question with which we are now confronted is, what is our place as the largest group of pediatricians in the world in reference to the over-all improvement of child health in this country? What should be our relations to the large, all-inclusive, medical organization, the American Medical Association? What should our relation be with government agencies at the national and state level? What part should we take in improving child health in our community? What part should we take in attempting to improve medical training in pediatrics, both graduate and undergraduate, and how can we assist in stimulating basic research in our segment of medicine? These are some of the things we as an Academy of Pediatrics must decide if we are to take what I

believe we all think is our rightful place in American medicine. After we decide upon some blueprint, then we must conceive a structure or an organization to carry out our objectives and finally acquire funds for their operation.

It is necessary first to redefine our objectives. As I understand the situation, we believe that there should be a voluntary body of physicians who can take part in planning for better child health. We have the American Medical Association and the American Public Health Association, both of which have great stakes in public health, but we are the only group with the great clinical interest and knowledge in the field of child health. My interpretation of the situation is that there are no two ways about it. We, who practice medicine, realize that our success depends upon our knowledge and our personal individual effort with each patient. By the same token, we must meet the challenge of the health of our respective communities. The position of the members of the Academy is a dual one: interest in individual children and leadership in all matters that concern the health of children.

In regard to the special phases of child health which the Academy should cultivate, we need the considered opinion of a special committee of the Academy. I should like to think that our greatest field concerned medical care. We should be the experts in this and should therefore take the initiative in extending and improving the quality of care. I should like to see a conference of representatives of the Children's Bureau, of the American Public Health Association, the American Medical Association, and the Academy at which some general confines of interests could at least for a period be determined. It is readily seen that the American Public Health Association would be interested in the field of immunization, food, water control, which integrates perfectly with our field. In this connection, our brochure on immunization practices would have greater publicity if it could be a joint undertaking.

The relation of the American Academy of Pediatrics to the American Medical Association is a matter that might well be given further thought. It has precedent in other branches of medicine. It certainly is true that the American Medical Association is the mouthpiece of American medicine. We are in no sense a competitive group but we do feel that when matters concern children's health we should take the leadership and be the authorities in the field. In general, I think matters of policy which seem important to us should be worked out in cooperation with the large organization. This by no means indicates that the Academy cannot act independently if the circumstances warrant it—if we feel that the health of children is at stake.

Any attempt to assume a position of leadership in child health or in fact any ambition to retain leadership brings us face to face with government agencies such as the Children's Bureau and the state departments of maternal and child health which receive large funds from the Children's Bureau. It seems pertinent to express the philosophy underlying the activities of the Children's Bureau and contrast it with that of the Academy. Last year at the annual meeting of the American Public Health Association we heard Dr. Martha Eliot,[3] then Assistant to the Chief of the Children's Bureau, say: "Because our children's needs are urgent, I believe that it is a public responsibility to see that all services and facilities necessary to meet these needs are made available as rapidly as possible. The only way we can be sure of doing this is through a public program, one that does not involve a 'means test,' one that is as freely available to mothers and children as is our public education system." This is not an occasion to discuss the "means test" nor the welfare state but it is pertinent to say that we of the American

Academy of Pediatrics do not believe that such a system as advocated by Dr. Eliot would give better medical care to the children of our country under the present conditions. It is needless to reiterate that the Academy has officially endorsed the use of federal aid for those unable to meet necessary costs. The Academy is opposed to assistance to those who can pay for their medical care. Our relations with the Children's Bureau are so important that it seems pertinent to review briefly their history as a background for further thought. The Children's Bureau came into being in 1912 under a statute "to investigate and report upon all matters pertaining to welfare of children and child life among all classes of people." It certainly has departed far from this objective. In 1921, when the Sheppard-Towner Act was passed, a new phase of activity was introduced and this was supported by the founding of our Academy. Here we had a public health program limited in respect to age and sex. The government established a separate department to promote public health for women to the exclusion of men, and for children under a given age to the exclusion of those older. In 1935, as a part of the Social Security Act, the function of the Children's Bureau underwent further enormous expansion. Thus, there came into being the Children's Bureau as we know it today, with little resemblance to its original intent of a Bureau "to investigate and report." Now, it is essentially a service agency whose purpose is to extend and improve services for promoting the health and welfare of children, "especially in rural areas and in areas of need." The extent of its activities in the field of health can be measured in terms of dollars. For the current fiscal year, the Children's Bureau operates under a congressional appropriation of $11,000,000 for maternal and child health services, an additional $7,500,000 for crippled children's services, and $3,500,000 for child welfare services.

With this background, we immediately see that this government agency has become a virtual dynasty, exerting a powerful influence upon the destiny of children in our country. Because of the power which the citizens of this country have directly or indirectly given the Children's Bureau, we must, as an organized body, also interested in circa one third of the people of our country, have available leadership to help direct this power. The Academy believes that its Fellows are the group who are actually rendering care to children and should have a definite part in directing this at all levels. The Academy believes that private as well as government aid is essential to better distribution of medical care. We believe that progress is dependent upon the initiative of voluntary organizations like the Academy. We do not believe that our government agencies should dictate how we are to bring up our children and tell us we should have "morning prayers." The Children's Bureau should not dominate but should aim to direct.

I have made rather detailed reference to the Children's Bureau because it seems to me that this illustrates one of the important fields in which Academy leadership is not only important but urgent. It should be clearly recognized that the federal agency is, in my opinion, most desirous for friendly and effective cooperation with the Academy in matters which concern better child health. I am one of those who believes that the only way to improve child health is to work in cooperation with agencies such as the Children's Bureau. Furthermore, I believe that this has been done and can be done. The Study of Child Health Services is an excellent illustration of a cooperative enterprise between the U. S. Public Health Service, the Children's Bureau and the Academy, and proves conclusively that with proper directorship on our part a great deal of fundamental work can be done. No one who has had any experience with the Children's Bureau can question the sincerity of the department and no one can ever question the idealism and loyalty of

its staff. It is certainly true that they have made mistakes and I am certain that they would admit this but one must also remember that they have assumed responsibility and initiated plans for child health many times because voluntary organizations did not take the initiative in planning. Our Study of Child Health Services has, in my opinion, opened an era during which the government agency interested in child health and voluntary or private groups interested in this field cooperated successfully.

There are areas where leadership in child care by an organization such as the Academy is particularly urgent and where there exists special opportunity for cooperation with other agencies. Among these is pediatric education. The Academy has already shown great interest and leadership in this area by demonstrating the needs for more and better training in pediatrics at the under- and postgraduate levels. Following our leadership, organized medicine in this country has espoused the cause of medical education and has suggested the needs of financial aid from private and federal sources. Our "Child Health Services and Pediatric Education," published by the Commonwealth Fund, is unique in the annals of medicine for its factual data, its thoroughness and its recommendations. It affords an excellent illustration of the status of teaching of practically any segment of medicine. The Academy has not only taken leadership in improving medical education but has adopted positive measures to improve better education of those who will give the care. The Academy has a singular opportunity in continuing its interest in pediatric education.

There are many other fields where the Academy can take its rightful place in American medicine. These are so many and so fundamental that we are in danger of embarking upon too many and becoming authorities in none.

It is all very well to talk about so-called leadership in the field of child health as sponsored by the Academy of Pediatrics, but this demands at least two important factors: one, an organization which can give necessary time and thought to planning of policies and, secondly, funds for the administration of executive affairs. At the present time, the Academy of Pediatrics is organized in such a way that this leadership which is necessary for cooperation with government agencies, with other organized medicine, with state organizations, and with local units is not possible. It has been done during the past few months by a temporary committee of the Academy but this lacks permanency. No organizational plan which may be brought forth will be complete and no plan should be advocated in haste, but it is urgent that such a plan be adopted and steps be taken immediately for its further development. Such a plan recognizes the necessity for the services of a Fellow of the Academy who can give his time unreservedly to the important activities of the organization. He, through the committees of the Academy, should be able to direct, plan and take an active part in formulating services for better medical care of children throughout the United States.

In order to carry out any such plan which will give us better leadership, it is necessary, as you well know, to have funds for this purpose. It is my own personal feeling that funds for this aspect of our Academy activities should not be derived, except possibly in a small part, from the members of our organization. This is a function which should be financed by the public, just as our educational institutions demand funds from private and other sources for their successful operation. These funds, of course, should be under the complete direction of the Executive Board and Officers of the Academy. Furthermore, it should not be the duty of the proposed Executive Secretary to collect these funds.

In conclusion, my experiences as President of the American Academy of Pediatrics

have given me added conviction of the importance of voluntary organization of medicine. More particularly has it afforded a conclusive demonstration that our Academy offers a determining position in improving the over-all health of children in our country. This experience which you have made possible has shown the great and immediate need for the Academy to increase its stature as a leader in the area of child health. It has been unequivocally shown that governmental agencies at the national and state level, interested in problems similar to ours, not only are willing but have cooperated in a most effective manner with the American Academy of Pediatrics. Furthermore, national and state voluntary organizations, the American Medical Association and state medical societies, have recognized the Academy's authority in its field and worked in cooperation for its objectives. The Study of Child Health Services at all levels is testimony of these statements.

The Academy is faced with the challenge of opportunity and leadership for the improvement of child health in this country. It was for this purpose that the Academy was founded.

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STUDY OF PULMONARY HYALINE-LIKE MATERIAL IN 4117 CONSECUTIVE BIRTHS

Incidence, Pathogenesis and Diagnosis

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IN A PREVIOUS study of consecutive autopsies on stillborn and live-born infants it was observed that a large number of infants dying in the first four days after birth had hyaline-like membranes in their lungs.[1] Evidence was presented indicating that this "fibrinoid" material found lining the alveoli and in the bronchioles and alveolar ducts was almost certainly not "vernix membrane" as had been previously supposed but was possibly the result of some injury to the epithelium and walls of the terminal air spaces. The nature of the injury described in the investigation referred to above was not determined. The close resemblance of the lesion seen in the lungs of newborn infants to those seen in individuals who died as the result of pandemic influenza, acute pneumonia of coccal origin and rheumatic pneumonitis was pointed out. It also was pointed out that newborn infants with this type of pulmonary lesion were usually live-born premature infants who had no other good explanation for their deaths and whose mothers had had pregnancies that were remarkably free of serious complications.

The results of the study mentioned above were based on the postmortem findings in 79 infants, both stillborn and live-born. It was felt that additional information could be obtained by a study of the many factors which are known to affect the survival of newborn infants, such as birth weight, race, sex of the infant, mother's age and parity and the complications of pregnancy, labor and delivery. It was thought that such a study, if applied to a large group of infants including those that survived the neonatal period as well as those that died, might yield additional information on the relation between this pulmonary lesion and the survival of the newborn infant and might also throw more light on the pathogenesis of the lesion. Since the pulmonary lesion under discussion was considered to be a cause of death among live-born infants and since as a part of the present study a comprehensive survey of consecutive births and deaths was being undertaken, a critical analysis of the causes of fetal and neonatal mortality has been made; the results will be reported elsewhere.[2]

MATERIAL

All the stillbirths, live births and neonatal deaths that occurred at the University of Kansas Medical Center during the years 1944 to 1948, inclusively, were investigated. No infants born outside of the hospital were included in this study. The hospital records of all mothers who gave birth to premature infants, dead infants or to infants who died during the neonatal* period were examined. Included were the hospital records of all infants who weighed 2500 gm. or less at birth. The autopsy protocols of all infants that died in the neonatal period were examined and the lung

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* The neonatal period included the length of time each baby spent in the hospital following birth. For most full term infants this was a period of 9 or 10 days; for premature infants, the period was much longer. Deaths occurring in premature infants more than 30 days old were not counted as neonatal deaths.

TABLE I

STILLBIRTHS AND NEONATAL DEATHS AND DISTRIBUTION OF HYALINE-LIKE MATERIAL IN LUNGS OF AUTOPSIED INFANTS IN 4117 CONSECUTIVE BIRTHS ACCORDING TO BIRTH WEIGHT

Birth wt.	Total births	Stillbirths*			Total live births	Neonatal deaths		
		No.	Autopsies			No. and fatality rate	Autopsies	
			Total	With hyal.			Total	With hyal.
1,000 gm. or less	22	2	0	0	20	17 (85%)	14	1
1,001–1,500 gm.	36	7	4	1	29	13 (45%)	12	8
1,501–2,000 gm.	91	10	4	0	81	18 (22%)	13	9
2,001–2,500 gm.	256	11	3	1	245	9 (3.6%)	8	3
2,501–3,000 gm.	1012	13	2	0	999	16 (1.6%)	14	6
3,001 gm. or more	2700	23	9	1	2677	12 (0.4%)	10	1
Total	4117	66 or (1.6%)	22	3†	4051	85 (2.0%)	71	28

* Stillbirths include 32 intrapartum deaths and 34 antepartum deaths; maceration was present in all fetuses born antepartum.

† All 3 fetuses died during labor.

sections were re-examined in all cases. In a similar manner the postmortem material on all stillborn infants was studied. Some of the infants in the present report were included in a previous investigation.[1] The infants in this study were under the complete care of the Pediatric Service from the time they first entered the nursery.

RESULTS

Incidence of Pulmonary Lesions

There were 66 stillborn and 4051 live-born infants included in the present study. Data on the births, deaths and the distribution of hyaline-like material in the lungs of autopsied infants are shown in Table I according to conventional birth weight groups. The conventional pattern was followed in order to show that the distribution of deaths, particularly neonatal deaths, was in close agreement with the low fatality rates that have been reported from other clinics in recent years.[2, 4] The data have been rearranged in Tables II and III in order to demonstrate results which were of statistical significance and which could not be shown in Table I because of the small number of deaths in each group.

The data in Table I on the incidence of hyaline-like material in autopsied stillborn and live-born infants in the various weight groups have been combined and compared in Table II. Infants who weighed 1000 gm. or less at birth were not included in Table II since they formed but a small group and the pathologic findings were different from those seen in more mature infants.[4, 5] It can

TABLE II

INCIDENCE OF HYALINE-LIKE MATERIAL IN LUNGS OF AUTOPSIED STILLBORN AND LIVE-BORN INFANTS WEIGHING OVER 1000 GM. AT BIRTH

	Stillbirths	Neonatal deaths
Autopsies	22	57
Autopsies with hyaline	3	27
Per cent	13.6	47.3

be seen from Table II that hyaline-like material was observed in only 3 or 13.6% of 22 autopsied stillborn infants as compared to 27 or 47.3% of 57 autopsies done on infants dying in the neonatal period. This is a statistically significant difference ($P<.02$).* The contrast was even greater, because the hyaline-like material in the lungs of stillborn infants was present only in small amounts, while in a majority of those dying after birth the amount of hyaline-like material was much greater. These findings are in agreement with those reported in an earlier investigation of a series of consecutive autopsies on stillborn and newborn infants.[1]

Inspection of the data on live-born infants in Table I suggested that there might be some relationship between birth weight and the occurrence of hyaline-like material in the lungs. The data have been combined in Table III in order to obtain larger samples. There were 110 live-born infants who

TABLE III

INCIDENCE OF HYALINE-LIKE MATERIAL IN LUNGS OF LIVE-BORN INFANTS AS DETERMINED BY AUTOPSY STUDY ACCORDING TO BIRTH WEIGHT

Birth wt. kg.	Births	Deaths	Autopsies	Autop. with hyaline	% live births with hyaline
1–2	110	31	25	17	15.0
2–3	1244	25	22	9	0.7
3 or more	2677	12	10	1	0.03

weighed between 1 and 2 kg. at birth; hyaline-like material, as determined by postmortem examination, was present in 17 of them or 15%. Although the sample in Table I is small, there is suggestive evidence that the incidence of this lesion in infants who weighed between 1001 and 1500 gm. was even greater than 15%, as there were 8 out of a total of 29 live-born infants in this group who had such changes in the lungs. The incidence of hyaline-like material was significantly less ($P<.01$) in the group of 1244 live-born infants whose birth weights ranged from 2 to 3 kg., being present in 0.7% of the live births as judged from the autopsy material. By the same criteria the incidence among the 2677 infants who weighed over 3 kg. at birth was 0.03%, which is significantly less than the incidence in the other 2 weight groups ($P<.01$).

Although the number of autopsies in this study was small, inspection of Table I indicates that hyaline-like material was not likely to be encountered in autopsies on live-born infants who weighed less than 1 kg. or more than 3 kg. There were 24 such autopsies and only 2 or 8% showed these changes, while 26 or 55% of the 47 autopsied infants who weighed between 1 and 3 kg. at birth had hyaline-like material in their lungs. This is a significant difference ($P<.01$).

The data on live births, neonatal deaths and the distribution of hyaline-like material in white and Negro infants are compared in Table IV. It is seen that the infants in this study were about equally divided between the 2 racial groups, there being 2027 white and 2004 Negro infants who weighed over 1 kg. at birth. The distribution of hyaline-like material was greatest in the lowest weight groups in both races. There were no significant differences between the 2 races except in the group that weighed between 2 and 3 kg. at birth. In this group the incidence of hyaline-like material was 1.5%

* The significance of the difference in this and subsequent samples was determined by the Chi Square Method and P was determined from Fisher's table of X^2 using Yates' adjustment for small numbers.[6]

among 527 white infants and 0.1% in 717 Negro infants, the difference being statistically significant ($P<.02$). This probably does not represent a true racial difference, but rather is related to the fact that a high proportion of Negro infants who weighed less than 3 kg. at birth were more mature than white infants of comparable birth weights.

Relation of Clinical Factors to Occurrence of Hyaline-like Material

There were 28 live-born infants in this study who had hyaline-like material in their lungs; all but 1 of these weighed over 1000 gm. at birth. There were 30 live-born infants who died during the neonatal period whose lungs were found not to have this pulmonary lesion; all of these infants weighed more than 1000 gm. at birth. Many of the clinical factors relating to the pregnancies, labors and deliveries of the mothers and to the clinical courses of the infants in these 2 groups have been investigated. The results are shown in Tables V, VI and VII.

The 2 groups of infants shown in Table V, 1 with and 1 without hyaline, are not entirely comparable. There were more white than Negro infants in the group with hyaline-like material in their

TABLE IV

INCIDENCE OF HYALINE-LIKE MATERIAL IN LUNGS OF LIVE-BORN WHITE AND NEGRO INFANTS ACCORDING TO BIRTH WEIGHT

Birth wt. kg.	Births	Deaths	Autopsies	Autopsies with hyaline	% live births with hyaline
Live-born white infants					
1–2	49	17	13	10	20.4
2–3	527	18	15	8	1.5
3 or more	1451	8	6	1	0.06
Live-born Negro infants					
1–2	61	14	12	7	11.4
2–3	717	7	7	1	0.1
3 or more	1226	4	4	0	0.0

lungs, while in the group without hyaline the number of white and Negro infants was equal. There is a significant difference in the number of infants who weighed under 2 kg. in the 2 groups. There were 18 out of 28 infants who had hyaline-like material in their lungs and weighed under 2 kg. at birth, as compared to 8 out of 30 in the group which did not have this pulmonary lesion ($P<.01$). Otherwise, the factors shown in Table V appeared to have no relation to the presence or absence of hyaline-like material in the lungs of these infants. The parity of the mother did not seem to be a significant factor. Although 7 of the 28 infants with hyaline were born to primiparas as compared to 13 of the 30 infants without hyaline, this is not a significant difference. The mothers' ages were evenly distributed between the 2 groups. There evidently was no difference in the length of the mothers' labors; 13 of the 28 infants with hyaline were born after 8 hrs. or less of labor and 16 of the 30 infants without hyaline were born after a similar interval. There was no apparent difference in the length of time that elapsed between the rupture of the mothers' membranes and the births of the infants in the 2 groups; less than 4 hrs. elapsed in 15 of the 28 infants with hyaline and in 16 of the 30 infants without hyaline. The type of anesthesia was essentially the same in the 2 groups, consisting of nitrous oxide in two thirds of the cases in each group. The use of analgesics was also comparable in the 2 groups; none was used in 18 of the 28 infants with hyaline and in 17 of the 30 infants without hyaline. There were no significant differences in the methods of delivery in the 2 groups; 15 of the 28 infants with hyaline and 13 of the 30 infants without hyaline were born after normal spontaneous cephalic deliveries; breech extraction was the method by which 6 of the former and 8 of the latter group were born; 5 mothers of infants with hyaline and 3 mothers of infants without hyaline were delivered by elective cesarean section. Thirteen of the 58 autopsied infants were born following the induction of labor or by elective cesarean section; there were only 3 of the 13

infants whose lungs contained large amounts of hyaline-like material. There were no significant sex differences in the 2 groups, there being 17 in each group who were males.

There was a strikingly low incidence of seriously complicated pregnancies and labors among mothers who bore infants with hyaline-like material in their lungs and a high incidence in mothers whose infants did not show such findings. Nineteen of the 28 pregnancies for which data are shown in Table VI were free of complications, both during pregnancy and labor; 4 of the 9 remaining pregnancies were complicated as follows: schizophrenia (Case 4), achondroplasia (Case 6), twins

TABLE V

COMPARISON OF CLINICAL FACTORS IN 58 MOTHERS AND THEIR AUTOPSIED INFANTS ACCORDING TO PRESENCE OR ABSENCE OF HYALINE-LIKE MATERIAL IN LUNGS

28 infants with hyaline		30 infants without hyaline
	Race	
20	white	15
8	Negro	15
	Parity of mothers	
7	para 1	13
11	para 2	7
3	para 3	4
7	other	6
	Mothers' ages	
3	under 20	6
21	20–29	17
4	over 29	7
	Duration of Labor	
13	8 hrs. or less	16
9	over 8 hrs.	9
5	no labor	3
	Membranes ruptured before delivery	
15	less than 4 hrs.	16
6	more than 4 hrs.	8
5	unruptured	3
2	undetermined	3
	Anesthesia	
20	nitrous oxide	19
2	spinal	4
4	undetermined	4
2	other	2
	Analgesia	
18	none	17
3	nitrous oxide	5
1	morphine	2
5	undetermined	6
1	other	0
	Method of delivery	
15	spontaneous cephalic	13
6	breech extraction	8
5	ces. section (elective)	3
2	other	6
	Sex of infant	
17	males	17
11	females	13
	Birth wt.	
18	under 2 kg.	8
10	over 2 kg.	22

(Case 13) and unexplained vaginal bleeding (Case 25), none of which necessarily would be considered as dangerous to the infant; in the other 5 cases there were serious maternal complications; Rh sensitisation (Case 3), diabetes mellitus and toxemia of pregnancy (Case 7), severe bromism (Case 9), diabetes mellitus (Case 14) and premature separation of the placenta and hydramnios (Case 21). It was not at all clear that the sensitisation of the mother to the Rh factor in Case 3 had anything to do with the infant's death. From the autopsy it seemed more likely that the baby had died because of the large amounts of hyaline-like material in the lung. In contradistinction to these findings was the high incidence of serious complications found in the group of infants whose lungs did not have hyaline-like material in them. There were only 13 pregnancies and labors in the group of 30 cases shown in Table VII that were uncomplicated. Three of the remaining 17 cases were complicated by (1) a positive serologic test for syphilis in the mother who had questionable treatment (Case 4), (2) a questionable sensitisation to the Rh factor (Case 15) and (3) twins (Case 18). None of these 3 maternal complications probably had any bearing on the outcome for

TABLE VI

CLINICAL AND AUTOPSY FINDINGS IN 28 LIVE-BORN INFANTS WHO HAD HYALINE-LIKE MATERIAL IN THEIR LUNGS

Case	Length of preg., days	Birth wt., gm.	Complications of labor and pregnancy	Degree of hyaline	Other significant autopsy findings	Autopsy	Age at death
1	267	3040	none	4+	none	complete	16 hr.
2	258	2875	none	1+	excessive extramedullary erythropoiesis	complete	7 hr.
3	256	2890	Rh sensitisation	4+	excessive extramedullary erythropoiesis	complete	33 hr.
4	261	2920	schizophrenia	4+	bronchopneumonia	complete	63 hr.
5	245	2610	none	1+	none	no brain	10 hr.
6	278	2925	achondroplastic dwarf	1+	achondroplastic dwarf	no brain	24 hr.
7	247	2750	diabetes mellitus; tox. pregnancy	1+	none	no brain	1 hr.
8	176	2050	none	2+	sclerema	complete	46 hr.
9	?	2065	acute psychosis; bromism	4+	none	complete	44 hr.
10	246	2050	none	4+	none	complete	30 hr.
11	225	1800	none	4+	cerebral hem., intraventricular, subdural, subarachnoid	complete	20 hr.
12	?	1575	none	4+	cerebral hem., intraventricular	complete	20 hr.
13	258	1685	twins	4+	none	complete	28 hr.
14	?	1775	diabetes mellitus	4+	none	complete	28 hr.
15	?200	?	none	3+	none	complete	9 hr.
16	?171	1900	none	3+	none	complete	12 hr.
17	219	1815	none	4+	none	no brain	6 hr.
18	208	1550	none	4+	none	complete	5 hr.
19	200	1535	none	3+	none	complete	33 hr.

TABLE VI—(*continued*)

Case	Length of preg., days	Birth wt., gm.	Complications of labor and pregnancy	Degree of hyaline	Other significant autopsy findings	Autopsy	Age at death
20	?	1350	none	2+	cerebral hem., intra-ventricular	complete	26 hr.
21	205	1190	prem. sep. plac., hydramnois	4+	none	complete	6 hr.
22	212	1290	none	3+	sclerema; broncho-pneumonia	complete	84 hr.
23	231	1355	none	4+	coarctation of aorta	complete	7 hr.
24	190	1175	none	1+	none	no brain	8 hr.
25	221	1380	vaginal bleeding (no cause found)	4+	hydrops fetalis	complete	11 hr.
26	208	1305	none	1+	none	complete	5 hr.
27	?173	1480	none	4+	none	complete	24 hr.
28	191	980	none	2+	sclerema	complete	46 hr.

the infants. Compared to 5 serious complications observed in Table VI there were 14 recorded in Table VII as follows: 3 instances of long hard labors, either in the 1st or 2nd stage (Cases 3, 5 and 27), 2 premature separations of the placenta (Cases 24 and 29), 1 prolapse of the cord (Case 17), 3 toxemias of pregnancy (Cases 16, 25 and 26), 2 instances in which Rh sensitivity developed in the mothers (Cases 13 and 14), 1 mother with bronchopneumonia at term (Case 9) and 1 case of hydramnios (Case 28). The difference in incidence of seriously complicated pregnancies and labors in the 2 groups is statistically significant ($P<.05$). It is clear that the large number of infants in the low birth weight groups with hyaline-like changes in their lungs was not caused by an increased incidence of serious complications of pregnancy or labor in the mothers of these infants.

Equally striking as the difference in incidence of serious maternal complications in the 2 groups of infants in Table VI and VII was the incidence of "negative" autopsies. In Table VI there were 16 autopsies which showed no other significant finding except the hyaline-like material to account for the death of the infants; in 4 of the 16 autopsies the central nervous systems were not examined. In 2 other instances, Cases 2 and 3 in Table VI, it is doubtful whether the so-called "other autopsy findings" can be considered as significant factors in the deaths of the respective infants, leaving 10 cases in which it is possible that death might have been caused by "other" factors than the hyaline-like material in the lungs. Among the 10 cases there were 3 in which cerebral hemorrhage was found at autopsy (Cases 11, 12 and 20), 3 of sclerema (8, 22 and 28), 1 bronchopneumonia (Case 4), 1 achondroplastic dwarf (Case 6), 1 coarctation of the aorta (Case 23) and 1 hydrops fetalis (Case 25). In contradistinction to these findings were the observations made on infants without hyaline-like material in their lungs. As shown in Table VII, there were 6 autopsies which showed no significant findings (Cases 4, 5, 16, 17, 26 and 30). There were 3 of the 6 autopsies in which the brains were not examined. In 2 additional instances (Cases 15 and 24) there were questionable findings; in Case 15 the diagnosis of erythroblastosis fetalis was questioned and in Case 24 there was some doubt concerning syphilis in the autopsy, although the mother was untreated and the

TABLE VII

CLINICAL AND AUTOPSY FINDINGS IN 30 LIVE-BORN INFANTS WEIGHING OVER 1000 GM. AT BIRTH WHO HAD NO HYALINE-LIKE MATERIAL IN THEIR LUNGS AT POSTMORTEM

Case	Length of preg., days	Birth wt., gm.	Complications of labor and pregnancy	Significant clinical and autopsy findings	Autopsy	Age at death
1	285	4055	none	extensive thrombosis of intracerebral veins with hem.	complete	89 hr.
2	?	3850	none	"suffocated in crib"	complete	56 hr.
3	?	4200	labor 52 hr.	"45 min. to resuscitate at birth"	complete	10 hr.
4	241	3005	4+ serology, ? of any treatment	none	no brain	7 days
5	300	3960	labor—62 hr., incision of cervix	none	complete	few sec.
6	?	3375	none	anencephaly	complete	68 hr.
7	?	3115	none	hydrocephalus; meningocele	complete	36 hr.
8	?	3225	none	cerebral hem., tear of tentorium	complete	5 hr.
9	?	3000	bronchopneum.	staph. sepsis; bronchopneumonia; kernicterus	complete	8 days
10	269	2695	none	hydrocephalus; meningocele; spina bifida	complete	123 hr.
11	269	2980	none	myelomeningocele	complete	8 days
12	280	2515	none	diaphragnatic hernia	no brain	2 hr.
13	277	2700	Rh sensitivity	kernicterus	complete	53 hr.
14	?	2550	Rh sensitivity	icterus gravis; kernicterus	complete	50 hr.
15	264	2880	?Rh sensitivity	?eryth. fetalis	no brain	84 hr.
16	260	2680	tox. of preg.	none	complete	36 hr.
17	283	2750	prolapsed cord	none	no brain	7 hr.
18	275	2160	twins	sclerema; polycystic kidney; cerebral atrophy	complete	62 hr.

TABLE VII—(*continued*)

Case	Length of preg., days	Birth wt., gm.	Complications of labor and pregnancy	Significant clinical and autopsy findings	Autopsy	Age at death
19	241	2310	syphilis	cerebral hem., subdural; syphilis	complete	16 hr.
20	?	2040	none	bronchopneumonia	complete	75 hr.
21	278	2400	none	cirrhosis of liver; E. coli sepsis	complete	15 days
22	239	2310	none	cerebral hem., subtentorial; focal pneumonia	complete	9 hr.
23	218	1900	none	sclerema; pneumonia; talipes-equino-varus	complete	100 hr.
24	209	1880	syphilis; prem. sep. placenta	? syphilis	complete	15 min.
25	256	1960	tox. of preg.; twins	porencephaly; microcephaly	complete	25 days
26	242	1685	tox. of preg.	none	no brain	38 hr.
27	221	1440	long second stage of labor	bronchopneumonia	complete	31 hr.
28	198	1060	hydramnios; twins	hydrocephalus	complete	43 hr.

placenta was considered to show definite syphilitic changes on microscopic section. In the 22 remaining cases there were clear cut explanations for the infants' deaths. Eight of the 22 infants had congenital malformations which were of a serious enough nature to account for their deaths; in 7 of these the central nervous system was involved (Cases 6, 7, 10, 11, 18, 25 and 28) and in the 8th infant (Case 12) a diaphragmatic hernia was found; cerebral hemorrhages of a severe degree were found in 5 infants (Cases 1, 8, 19, 22 and 29); 3 other infants had cerebral involvement in the form of kernicterus (Cases 9, 13 and 14); in 2 additional infants (Cases 2 and 3), while there were no striking changes in the postmortem examinations, the explanation of their deaths appeared to be clear cut, since 1 was found "suffocated" in his crib (Case 2) and the other infant was resuscitated following delivery only after 45 min. of constant effort; the 4 remaining infants had infections as follows: Cases 20 and 27, bronchopneumonia, Case 21, septicemia associated with cirrhosis of the liver and Case 23, pneumonia associated with sclerema. Several of the 22 infants had more than 1 significant finding; no claim is made that the findings referred to above were necessarily the only causes of death. In summary, there were 16 autopsies out of the 28 recorded in Table VI as compared to 6 out of 30 in Table VII which were free of significant findings (other than the hyaline-like material in the lungs of the infants shown in Table VI). Statistically this is a significant difference ($P<.01$).

If the serious maternal complications of pregnancy and labor are taken into account along with the significant clinical and autopsy findings in the infant, it can be seen from an inspection of Tables VI and VII that there are considerable differences. There were 12 infants listed in Table VI who were born to mothers whose pregnancies and labors were free of serious complications and whose autopsies showed no significant findings except for the pulmonary lesions; in 9 infants the amount of hyaline-

like material in the lungs was marked, 3 to 4 plus (Cases 1, 10, 13, 15, 16, 17, 18, 19 and 27), and in 3 it was minimal (Cases 5, 24 and 26). In marked contrast to the above was the fact that there was only 1 case in Table VII in which there were both no significant autopsy findings and the mother's pregnancy was free of complications (Case 30); it is to be noted that this infant's birth weight was 1040 gm., the lowest in the group of 30 cases, and near to the birth weight group in which the chances for survival are poor and the cause of death is usually just "prematurity." The number of cases in Table VI which were found to be free of both serious maternal complications and significant autopsy findings (other than hyaline) is significantly greater than was observed in Table VII ($P<.01$).

There are important differences in the time that death occurred in the 2 groups of infants reported in Tables VI and VII. Twenty-six of the 28 infants in Table VI died within 48 hrs. of birth; 17 died in the 1st 24 hrs. Among the 30 infants recorded in Table VII there were only 14 who died in the 1st 48 hrs. and 9 who died during the 1st 24 hrs. In this series if an infant weighed over 1000 gm. and died in the 1st 48 hrs. of life there was a 65% chance that the autopsy would show hyaline-like membranes in the lungs based on the fact that 26 out of the 40 infants shown in the 2 tables who survived less than 48 hrs. had such pulmonary lesions. The chances were the same in this series if the infant died during the 1st 24 hrs. of life, based on the observation that 16 of 25 infants dying in this interval had such lesions in their lungs. If the infant died between 48 and 96 hrs. after birth, the chances of finding hyaline-like material in the lungs fell to just over 20%, since only 2 out of 10 infants dying in this period had these changes. No infant dying after 96 hrs. of age was found to have these changes in the lung.

The possibility that the hyaline-like material might be aspirated food is eliminated, since 22 out of 28 infants reported in Table VI received no food prior to their deaths.

An investigation was made on the possible occurrence of hyaline-like material in the lungs of siblings of infants who were known to have or not to have this type of pulmonary lesion. The mothers of 21 infants recorded in Table VI were multiparas who had a total of 37 live-born infants in addition to the 21 included in Table VI; there were 9 neonatal deaths in this group of 37 infants; 1 was a monster, another died whose mother had a placenta previa and a 3rd had erythroblastosis fetalis; 3 additional unexplained deaths occurred in 1 family, all of which took place in the 1st 2 days of life; there were 3 deaths that were unaccounted for; unfortunately no autopsies were obtained in any of the 9 infants. There is insufficient data in the present study to determine whether there is any tendency for this lesion to repeat itself from 1 sibling to the next. There were 17 infants listed in Table VII whose mothers were multiparas; a total of 34 infants were born to these mothers in addition to the ones recorded in Table IV and there were 4 deaths, 3 of which could be accounted for on the basis of the mother's Rh sensitisation, leaving 1 death unaccounted for in a twin. Again, it is felt that this is insufficient material on which to base an opinion.

Diagnosis

The diagnosis of hyaline-like material in the lungs of live-born infants who die can be made with a fair amount of certitude on a statistical basis before the postmortem study is done. In Table II it was shown that almost 50% of all autopsies done on live-born infants with a birth weight over 1000 gm. will show this change. It was further shown that 65% of all infants weighing over 1000 gm. at birth dying in the 1st 48 hrs. of life were found to have such findings in their lungs. The elimination of all infants in Table VI and VII whose mothers' pregnancies and labors were seriously complicated and of all infants who had some clinically recognized disease or defect, such as kernicterus, sepsis, sclerema or severe congenital anomaly, would raise the incidence of positive pulmonary findings from 65 to 90%. On the other hand, if the mother did have some serious complication of labor or pregnancy or if the baby did have some clinically recognized defect or disease of a serious nature, weighed over 1000 gm. at birth and died in the 1st 48 hrs. of life, the chances were 80% that the infant would not be found to have hyaline-like material in the lungs. These data are based on the fact that there were only 7 cases in Table VI as compared to 28 in Table VII which fell into this category.

The question arose as to whether a correct diagnosis could be made from the symptoms and physical examinations of the infants alone. Consequently, a study was made of the symptoms exhibited by infants dying with hyaline-like material in their lungs. The study was limited to the 9 infants in Table VI who had 3 to 4 plus hyaline in their lungs but no other significant findings and who were born following uncomplicated pregnancies and labors. The mothers of 6 of these infants received no analgesia; 7 mothers had nitrous oxide anesthesia and 2 had none. Respiratory difficulty was

marked throughout the few hours they lived. Although the respirations were frequently weak, all 9 of the infants at some time exhibited labored breathing. In most of them there was marked retraction of the lower part of the chest wall on inspiration. There was great variability in the onset of this type of dyspnea; in some infants it was present at birth and later would diminish and in others it did not appear until several hours after birth. A few required resuscitation at birth and the course of some infants was marked by recurrent periods of failing respirations and cyanosis for which they repeatedly received chemical stimulants and artificial respiration. The infants' cries were usually weak. Mucous in small to large amounts was present. One infant spit up bloody mucous and another spit up bright red blood repeatedly, as much as 1 or 2 teaspoonfuls at a time. The infants were kept in heated incubators into which 100% oxygen was piped in large amounts, which was routine treatment for all premature infants in the 1st 24 hrs. of life. Physical examination revealed infants in varying stages of vigor and the examinations of the lungs were reported as showing fine rales, varying amounts of localized dullness to percussion and suppression and exaggeration of breath sounds. There were no pathognomonic symptoms or signs and there was nothing about the clinical courses of these infants that would sharply distinguish them from infants who were found to have other serious diseases, such as those involving the central nervous system. It should be remembered that the symptoms described here in the infants dying with hyaline-like material in their lungs were recorded by individuals who were completely unaware of the existence of the pulmonary lesion or its importance. Possibly with closer observation in the future the symptoms and physical findings will become more clearly defined.

There was a striking contrast between the severity of the respiratory difficulties seen in infants dying with large amounts of hyaline in their lungs and infants who survived in the present study. A careful study of the hospital records of the 318 premature infants who survived the neonatal period revealed only 10 who were reported to have had labored breathing or retraction of the chest wall on inspiration during the 1st 2 days of life and in 7 of the 10 cases there had been serious complications of pregnancy or labor of the type which in this study have been shown to be usually lacking when hyaline-like material is present. Cyanotic episodes of a transitory nature unattended by respiratory embarrassment were observed in 16 additional infants in the 1st 2 days of life. The low incidence of respiratory difficulties in this series can be explained in large part by the fact that analgesia was rarely used in any form. No analgesia was given to the mothers of 202 of the 318 premature infants; the mothers of 79 additional infants had nitrous oxide and oxygen as analgesia. Eighteen mothers were delivered under spinal anesthesia, leaving only 19 infants whose mothers received some analgesic drug. The impression has been gained by the pediatric staff as a result of the facts brought out in this study that infants in these nurseries having labored respirations with or without retraction of the lower chest wall during the 1st 2 days of have an excellent chance of having hyaline-like material in the lungs and dying providing there has en no serious maternal complication and providing there is no other obvious disease or defect that can be diagnosed in the infant.

Discussion

There are several facts brought out in the present study. The pulmonary lesion under discussion had its greatest incidence among infants weighing between 1000 and 2000 gm. at birth with a diminishing incidence in higher weight brackets. There was a remarkable lack of obvious abnormalities in the pregnancies and labors of mothers giving birth to infants who were found at autopsy to have hyaline-like material in their lungs. There were significantly fewer concomitant diseases and defects among infants dying with this pulmonary lesion than among those who died and were found not to have hyaline-like material in their lungs. These facts were so sharply defined that it was possible to make a prediction as to which infants would be found at autopsy to have hyaline-like material in their lungs in almost 90% of the infants if they died in the first 48 hours of life.

The above facts suggest that the lungs of the fetus are peculiarly susceptible to some type of injury at a certain stage of development and that possibly the agent which causes the pulmonary injury also precipitates labor and birth. The injury probably occurs in utero, since hyaline-like material was found in the lungs of a few stillborn infants, although only in small amounts. Furthermore, it seems unlikely that the injury could be

produced after birth, since only five or six hours elapsed between the birth and death of several infants who were found to have large amounts of hyaline-like material in their lungs. Results of experiments on dogs exposed to cadmium chloride inhalations showed that at least 24 hours elapsed between the exposure and the production of hyaline membranes in the distal air spaces of their lungs.[7] During the first 24 hours after exposure the only changes noted were a necrosis and desquamation of the epithelium of the trachea, bronchi and bronchioles.

The concept that the agent which injures the lung also precipitates labor is an important one, although at present there is only circumstantial evidence to support it. If the etiologic agent merely induced changes in the lung without precipitating labor, one would expect to find the hyaline changes in stillborn premature infants in the same ratio as in live-born premature infants, but such was not the case in the present study. It also would be expected that the hyaline-like material would be distributed equally among live-born premature infants without regard to maternal complications of pregnancy and labor or to other types of diseases and defects in the infants. It was found in the present study that there was a significant difference in the incidence of the lesion with respect to these last mentioned factors. It is true that a few of the infants who at autopsy were found to have hyaline-like material in their lungs had other significant findings. These other findings consisted almost wholly of cerebral hemorrhages and sclerema, both of which are predominately found in premature infants. There was a singular absence of hyaline changes among premature infants dying with severe congenital malformations, which bear no relation to premature birth.

The nature of the agent that might have been responsible for the hyaline-like lesion in the lungs remains unknown. In a previous report the possibility that the lesion was caused by the aspiration of amniotic sac contents was considered as most unlikely, since the lesion was found in live-born infants and rarely in stillborn infants and because evidence of fat and epithelial cells, both of which are found in vernix caseosa, was notable by its absence in many lungs containing abundant hyaline-like material.[1] The recent reports suggesting that some premature births are related to deficiencies in the protein of the maternal diet are grounds for speculating as to whether this pulmonary lesion might be a deficiency disease.[4] The somewhat lower incidence of the lesion among Negro infants in this study, while not statistically significant, does not offer any support for this theory, since in general the nonwhite mothers entering on the obstetric service of this hospital come from economic groups that would be expected to have no better eating habits and no higher incomes than the white mothers. The resemblance of the lesion in the lungs of the newborn infants to that seen in older individuals dying with acute pulmonary infections of various kinds naturally suggests the possible role of infection as the etiologic agent. Study of the mothers' hospital records for evidence of infection was not helpful, but this is a factor that should be given further consideration. In view of the many different agents that have already been shown to be associated with the presence of hyaline-like membranes in the lungs of humans and animals, including radiation pneumonitis,[8] a wide search may be necessary before the etiology of this lesion in newborn infants is discovered.

Summary

A study has been made of 4117 consecutive births including 66 stillborn infants and 85 neonatal deaths. Autopsies were done on 22 stillborn infants and 71 infants dying during the neonatal period.

From the autopsy study of neonatal deaths it was found that at least 15% of all live-born premature infants weighing between 1000 and 2000 gm. at birth had hyaline-like material in their lungs. The incidence of the pulmonary lesion was found to diminish progressively as the birth weight of the infants increased, so that it was practically non-existent in infants weighing over 3000 gm. at birth.

It was found that 90% of all infants weighing over 1000 gm. at birth and dying in the first 48 hours of life had hyaline-like material in their lungs at autopsy providing their mothers' pregnancies and labors had been free of serious complications and providing that the infants themselves had no other clinically recognized disease or defect of a serious nature.

No relation was found between the presence of the pulmonary lesion and the race, sex, order of birth of the infant or the age of the mother and length or type of labor. The lesion was not produced by the aspiration of food.

The symptomatology of the infants dying with hyaline-like material in their lungs was characterized by marked respiratory difficulty, including retraction of the lower chest wall with inspiration. The symptoms were not pathognomonic, but few premature infants with similar symptoms survived.

The pathogenesis of this pulmonary lesion remains unknown. The theory is advanced, based on the facts brought out in this study, that the hyaline-like material in the lung is the result of an etiologic agent that not only injures the lung of the fetus, but also causes the premature birth of the infant so injured.

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SPANISH ABSTRACT

Estudio del Material Pulmonar parecido Hialina en 4117 Partos Consecutivos; Incidencia, Patogenesis y Diagnosis

Se ha hecho un estudio de 4117 partos consecutivos incluyendo 66 partos muertos y 85 muertes neotales. Se les hizo la autopsia a 22 infantes que nacieron muertos y a 71 infantes que murieron en el período neotal.

Del estudio de la autopsia de las muertes neotales se averiguó que por lo menos 15% de todos los infantes que nacieron prematuros pesando entre 1000 y 2000 gramos al nacer, tenían un material parecido hialina en los pulmones. Se encontró que la incidencia de la lesión pulmonar disminuye progresivamente a medida que el peso de los infantes aumenta, así es que casi no existía en infantes que pesaban más de 3000 gm. al nacer.

Se encontró que 90% de todos los infantes que pesaban más de 1000 gm. al nacer y que murieron durante las primeras 48 horas de vida, tenían el material parecido hialina en sus pulmones al hacerles la autopsia siempre que los embarazos y dolores de parto hayan estado libres de serias complicaciones y que los infantes mismos no hayan tenido otros defectos o enfermedades de naturaleza seria.

No se encontró relación entre la presencia de la lesión pulmonar y la raza, sexo, orden de nacimiento del infante ni con la edad de la madre ni duración o tipo de parto. La lesión no se redujo mediante aspiración de alimento.

La sintomología de los infantes que murieron con material parecido hialina en sus pulmones fué caracterizada por dificultad respiratoria marcada, incluyendo retracción de la parte inferior de la pared del pecho con inspiración. Los síntomas no fueron patognómicos, pero pocos infantes prematuros con síntomas similares vivieron.

Se desconoce aún la patogenis de la lesión pulmonar. La teoría avanzada basada sobre los hechos sacados de este estudio es que el material parecido hialina en el pulmón es el resultado de un agente etiológico que no solamente daña el pulmón del feto, sino que causa el nacimiento del infante asi dañado.

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TEACHING THE BROADER ASPECTS OF PEDIATRICS

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THE PHYSICIAN who cares for children and the parents who consult him tend nowadays to be less occupied in their visits with physical disease, more with growth and development, behavior problems, school and social adjustment. There are well known reasons for this shift, which include the minimizing of infection by means of sanitation, immunization and the antibiotic drugs, the increased awareness on the part of parents and physicians of the importance of fostering the child's total development and total adjustment, the interest in preventive psychiatry and psychosomatic medicine. The trend will probably continue, especially as more physicians are trained who are interested and helpful in these areas.

If pediatrics does not accommodate itself to the increasing desire of parents for preventive guidance, the vacuum might be filled by a new specialty, perhaps from within the field of psychology. In some ways this would seem a logical development, since the cost of training a physician to be competent in all aspects of child care tends to put his services beyond the means of many. But it would be an unfortunate backward step to divide again the child's emotional well-being from his physical well-being, to divide his development from his diseases, and to entrust them to two separate specialists.

At the present time departments of pediatrics and pediatric hospital services, in their training programs, are going on the assumption that the physician who practices pediatrics, part or full time, is the person who ought to treat the child's illnesses, immunize him, supervise his physical growth, guide his emotional development, especially in the early years, and be able to advise his parents whenever any problem arises, even though the assistance may consist only in knowing to which other expert or agency to refer him.

The means usually sought to broaden the training in all the emotional aspects of pediatrics is to add a child psychiatrist directly to the pediatric staff or at least to the psychiatric department of the medical school or hospital. His teaching province then covers such subjects as normal emotional development, the prevention and early treatment of behavior problems, psychosomatic medicine, the testing and significance of intelligence and aptitude, school adjustment, social adjustment, the management of the psychologic aspects of hospitalization, illness and the doctor-patient relationship.

This is an ideal method if it can be carried out. However, there are a number of difficulties to surmount. There is a great scarcity of child psychiatrists, especially of those familiar with pediatric problems and procedures. A psychiatrist's salary for part or full time is relatively high because his work is peculiarly time-consuming—he cannot compress his income-producing practice into a fraction of his working day. Relatively few pediatric departments have a budget that permits securing much of a psychiatrist's time. If the child psychiatrist's allegiance is to the department of psychiatry and he is located there, he may have little time left to work among and teach the pediatricians. If he functions only as a recipient of referrals from pediatrics his teaching value to

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pediatricians may be less than zero. He not only has no opportunity to teach them; he relieves them of the necessity of trying to cope somehow with the emotional problems they meet. All such cases can be comfortably evaded by sending them over to psychiatry.

But it would be a great mistake to assume that the possibility of teaching the broader aspects of pediatrics depends entirely on securing the time of a psychiatrist. There are many other professionals in every city and several in every hospital who know well one or more aspects of child nature and can make a real contribution to pediatric education if given a chance.

The pediatric social worker or the medical social worker in many hospitals is called on only when there is obvious need for financial assistance, such as for glasses or convalescent care. Yet her training and her knowledge of neighborhood families would enable her to make a dramatic case presentation of a current ward or clinic patient at pediatric staff meeting or case conference or teaching session. A wise public health nurse could do the same job. At case conferences observant ward nurses could regularly be called on to describe the child's behavior and emotional reactions during hospitalization. This would not only remind the medical staff of the patients' human side but also encourage the nursing staff to better observation and better psychologic care. If the hospital has the assistance of a school teacher or occupational therapist or play teacher, she can and should be invited to contribute to case conferences. This is stimulating to the medical staff and to her.

For a case conference it may occasionally be possible to arrange to have the child's nursery school teacher or grade school teacher come to the hospital or clinic to give the picture of his social and academic adjustment and something of his background. In appropriate cases it is usually simple to invite the social worker from the local family agency or children's agency, who may have extensive and revealing material on the child. Such agencies are not only willing but pleased to be included in such conferences.

Even though a children's hospital or clinic has no psychiatrist, psychologist or psychiatric social worker of its own, it may be able to borrow these specialists occasionally from a neighboring clinic, when a case turns up in the pediatric service which is found to have been worked up in a psychiatric clinic. One or more of the psychiatric team could be invited over to give a full case history. Or suppose that a child with an emotional problem has been discussed carefully in a pediatric conference with the full participation of a social worker from the hospital or the community and it is decided in the end that the complexity of the case warrants psychiatric investigation. The referral to a psychiatric clinic is made, and after the work-up has been completed the psychiatric team is invited to the pediatric conference for a full report. The fact that such a case has first been tackled, though incompletely, by the pediatric staff makes them much more receptive and eager for the psychiatric data.

For staff meetings or teaching sessions devoted to a topic rather than a case there is usually a great variety of experts in the community who can give a talk or contribute to a discussion of real importance and interest to pediatricians. There are classroom teachers, specialized teachers, remedial teachers, school guidance counselors, school administrators, psychiatrists, psychologists, psychiatric social workers, people from adoption agencies, foster home agencies, institutions for neglected, blind, deaf, crippled, delinquent or convalescent children, children's dentists, probation officers, attendance officers, judges of children's courts, boys' and girls' club directors. Such speakers cannot be invited at random. They should be judiciously picked for competence and vividness, steered into the right topic and drawn out in discussion. But when well chosen they can broaden the physician's awareness of children's special problems, general needs and the community's

resources. This knowledge is not only interesting but vitally important for pediatrics.

When interest is thoroughly aroused, it should be possible to arrange for actual observation, particularly on the part of pediatric interns and residents, of such activities as children's institutions, clubs, courts, schools. The value is least when a large group goes on brief sight-seeing tours, but increases with the smallness of the group, the length of observation and the opportunity to talk with the staffs. Every physician who is to care for children should have the experience of visiting, at least for several days, in an elementary school with some excellent teachers, to get a more objective view than he carries over from childhood of what school is like; how the teaching process works; the variety of methods used; the striking contrast between different children's abilities, personalities and adjustment; the relationship between teacher's attitude, classroom atmosphere and the children's behavior.

A few of the best organized training programs for pediatricians, pediatric nurses and child psychiatrists now include a considerable period in a first-rate nursery school, not simply for observation but for actual participation as an assistant teacher. Experience has shown that, when the supervision is good, this is one of the most effective means of teaching what a child is like, why he behaves and misbehaves, what he needs from adults and other children, and how he can be wisely managed.

There is one more important point. Medical students, interns, residents and junior members of the attending staff take their cue about what is important in pediatrics from the senior staff members. There is a tradition in many pediatric services that the younger staff men work in the outpatient department and well baby clinic for a number of years. Then those who deserve it are promoted to ward services. At that time or when they have achieved a more dignified age, they are excused from work in the outpatient department. The unfortunate implication is that the work of the clinic is drudgery and that the ward service is the essence, the cream of pediatrics. Most of us left our resident training to enter practice confident in our ability to get a needle into veins, to diagnose blood dyscrasias and to treat gastrointestinal intoxication. Yet we found ourselves poorly equipped to answer half the questions that parents asked us. It is in the outpatient department, in the well baby clinic and in the private office that the major part, the constructive part, of pediatrics is carried out. There is no reason whatsoever why the work there cannot be just as interesting, as challenging, as rewarding as ward work. But the pattern has to be set by the senior staff members—working there, teaching there, holding regular staff conferences there, showing enthusiasm for the cases there. Enthusiasm not just for diagnosing the unusual case—enthusiasm for trying to understand and solve the common, everyday problems that trouble children and parents everywhere.

SPANISH ABSTRACT

Enseñanza de Aspectos Más Amplios de Pediatría

La pediatría está incesantemente relacionada con el desarrollo físico y mental. Afortunados centros de entrenamiento pediatricos han agregado psiquíatras a su personal. Pero cuando esto es imposible, hay métodos sustitutos para enseñar los aspectos impresionables, sociales, psicosomáticos y pedagógicos del bienestar del niño. En las conferencias y sesiones de enseñanza del personal pediátrico se pueden invitar a participar, contribuir casos individuales, colaborar en programas de tratamiento, y explicar recursos de la comunidad. Estos incluyen enfermeras de hospital y salud pública, trabajadores sociales, personal clínico psiquiatrico cercano, maestros de escuela, etc. Los miembros del personal pediátrico de más expeiencia pueden dar el ejemplo mostrando interés en los problemas diarios de los niños en los departamentos de enfermos no hospitalizados y clínicas de niños buenos.

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BENZEDRINE® AND DEXEDRINE® IN THE TREATMENT OF CHILDREN'S BEHAVIOR DISORDERS

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THE PSYCHOLOGIC responses of children to benzedrine (racemic, [dl-], amphetamine) sulfate and its dextro-rotatory isomer (d-amphetamine) known commercially as dexedrine sulfate have been the subject of several communications appearing in the literature since 1937. No comprehensive summary of the comparative values of these two preparations in child psychiatry has as yet appeared. The present report, based on 12 years' clinical experience and involving observations on the behavior of more than 350 individual maladjusted children who were treated with these drugs for various periods while under psychiatric observation, has been prepared with the hope that it may prove a useful source of reference to pediatricians, psychiatrists and others interested in the clinical treatment of children's behavior disorders.

SURVEY OF THE LITERATURE

Benzedrine® (racemic amphetamine) and dexedrine® (dextro-rotatory amphetamine) are sympathomimetic amines, characterized particularly by their ability to stimulate the higher centers, particularly the cortex.[1, 2] Dexedrine® is generally considered to be the more potent in this latter respect.

Clinical experience with benzedrine®* in the field of child psychiatry was first reported by Bradley in 1937.[3] This was amplified by subsequent communications from Cutts and Jasper,[4] Lindsley and Bradley,[5] Bradley and Bowen,[6] Bender and Cottington,[7] Lindsley and Henry,[8] Bradley[9] and Bakwin.[10] In most of these reports the effects of benzedrine® on so-called "problem children" are contrasted to what is commonly observed in adults. In the latter this stimulating drug customarily produces a sense of well-being and mental alertness and an increase in psychomotor activity with commensurate decrease in drowsiness, listlessness, depression or fatigue. In children, however, where maladjustment is frequently expressed through symptoms of restlessness, noisiness, hyperactivity and distractability, the most dramatic observable effects of benzedrine® are a decrease in such symptoms and the appearance of what has been described as more "subdued" behavior. In one report[6] this was depicted as follows:

"Many children began to walk and move quietly in contrast to previous noisy running and rushing about. A number spoke in normal or lowered tones of voice instead of

From the Emma Pendleton Bradley Home, East Providence, R.I.

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* To avoid confusion, racemic amphetamine sulfate will be referred to by its commercial name "benzedrine®" in the text and dextro-rotatory amphetamine sulfate will be designated by its commercial name "dexedrine®."

shouting raucously. Some of these same children, instead of quarreling and arguing boisterously, began to avoid expressing differences of opinion or conducted their discussions in tones which were not offensive. In certain instances children appeared subdued because they began to spend their leisure time playing quietly or reading whereas formerly they had wandered aimlessly about antagonizing and annoying others."

While this dramatic and obviously clinically desirable response to benzedrine® was the most common reaction of children, some whose symptoms had been those of underactivity and withdrawal from social contacts appeared stimulated by the drug to a more active and successful participation in conventional childhood activities.

In a few children one or the other of the two reactions which have just been described were noted clearly only in the somewhat restricted area of the schoolroom, where, however, the result was dramatic acceleration of their academic progress. As might be expected in any pharmacologic study at the clinical level, a small minority of children have been noted to show no behavior response to benzedrine® in any setting.

Whenever any of the above reactions were observed they became apparent from 20 to 40 minutes after benzedrine® was ingested orally, seemed to be most intense for the ensuing 3 to 4 hours, persisted to a less extent for an approximately equal period thereafter and apparently disappeared by the following day. Fairly large oral doses (usually in the neighborhood of 20 mg.) were necessary to produce significant results, and where daily morning doses of this size were continued over periods of several months no evidence of tolerance and a practically insignificant incidence of seriously undesirable side effects were observed. Hypodermic doses of the same size produced more prompt but less persistent effects.[9]

In addition to these alterations in children's total behavior patterns the use of benzedrine® to bring about more specific psychologic responses in children has been reported. Bradley and Bowen[11] noted striking improvement in school adjustment and academic performance, particularly in arithmetic. Molitch and Poliakoff[12] found benzedrine® helpful in the treatment of enuresis. While preliminary reports[13, 14] suggested that benzedrine® might exert a favorable effect upon the psychometric scores of children, Bradley and Green[15] were able to demonstrate that this was an apparent rather than a real effect inasmuch as benzedrine® improved "readiness for testing" rather than intelligence itself.

A number of workers have studied the effect of benzedrine® on children showing electroencephalographic abnormalities.[4, 5, 8, 9] The findings in general indicate that behavior may become profoundly affected without commensurate changes in the electroencephalographic patterns. The definitely favorable effect of benzedrine® upon the behavior difficulties of children with convulsive disorders has been reported by Bradley,[16, 17] with the note that abnormalities in the EEG or the occurrence of seizures themselves were not particularly affected by the drug. However, other workers[18, 19] have reported favorable results from benzedrine® (and dexedrine®) upon the seizures themselves. Other reports have mentioned the results of benzedrine therapy in children with cerebral palsy[20, 21] and schizophrenia.[22]

Dexedrine®, which became available for clinical use some years later than benzedrine®, has been less frequently discussed as a therapeutic agent for maladjusted children. However, reports of its use experimentally in the laboratory and clinically with adults suggest that while its general effects are similar to benzedrine® it is approximately twice as potent in its influence upon psychologic activity. It has been recommended that

dexedrine® may be used in half the dosage anticipated for benzedrine® to bring about a therapeutic response and that the likelihood of undesirable side effects is thereby diminished.

The most commonly mentioned untoward effects of both benzedrine® and dexedrine® as far as their use in child psychiatry is concerned are their depressant effects upon the appetite and their frequent production of insomnia. The former characteristic has led to their use as adjuvants in the treatment of obesity, although this has been reported mainly on the basis of clinical work with adults rather than children.[23] Although both drugs tend to produce an elevation in blood pressure, which is sometimes a contra-indication to their administration to elderly, cardiac or hypertensive patients, this effect is distinctly less apparent in children[3] and may usually be disregarded. Pallor of the face, coldness of the extremities and other evidences of peripheral vasoconstriction are not infrequently observed as transient side effects for an hour or two after the drugs have been taken. Fine tremors of the extremities have also been reported. Most of the undesirable effects are of minor significance in the majority of children whose total adjustment becomes dramatically and favorably altered.

Material and Methods

The present study was carried out with children who were resident patients at the Emma Pendleton Bradley Home, a children's psychiatric hospital. In this setting, the importance of which for such a project has been previously emphasized,[3, 6] the patients were free on the one hand from the artificial limitations of a laboratory setting and on the other from many factors influencing social adjustment which in the community defy control and evaluation. All the children were under 13 yrs. of age, were for the most part of average or superior intelligence, and were under treatment for a wide variety of neuropsychiatric complaints. They were under the care and observation of an experienced staff of graduate nurses, teachers and other professional workers especially trained in evaluating and recording childhood behavior.

Each child in this study received daily oral doses of benzedrine® or dexedrine® for consecutive periods of never less than 7 days and usually of several weeks or months in duration. Medication was administered as a matter of routine hospital procedure and without comment by members of the nursing staff. Records of response to the treatment were part of periodic behavior notes written systematically at weekly or biweekly intervals for all patients in the hospital.

Subjects for these studies were 275 children (227 boys and 48 girls) who received benzedrine®, 113 patients (94 boys and 19 girls) who were given dexedrine®, and 82 individuals (72 boys and 10 girls) included in these 2 preceding groups, but who over separate periods were treated with each of the drugs. No other medication was administered during the periods of observation involved in the major part of these studies.

The material in all of its aspects has been considered from an essentially clinical and, it is hoped, an eminently practical point of view.

Observations

Dosage and Patient's Age

The present study deals only with doses upon which each child made his most favorable behavior responses in terms of the reactions noted above.

Table I shows the age distribution of children treated with benzedrine®, as well as the daily doses found most effectual for the various age groups. Table II portrays the same material for children treated with dexedrine®. Although the numbers of children appearing at the various age levels were influenced largely by the frequency with which children of various ages were available at the Bradley Home for this study, the data offers several definite conclusions.

In Table I it will be noted that nearly 4 times as many children were found to respond to benzedrine® 20 mg. daily more favorably than to any other single dose. Although by accepted clinical (adult) standards 20 mg. is a large amount it was found practical for children as young as 5 yrs. A daily dose of 10 mg. was found most effective in the next largest group of children, possibly a little more predominantly so on children from 3 to 7 yrs. of age. Relatively few children required

TABLE I

NUMBER OF MALADJUSTED CHILDREN RECEIVING VARIOUS DAILY DOSES OF BENZEDRINE SULFATE ARRANGED IN GROUPS ACCORDING TO AGE

Daily dose	Age in yrs. 3	4	5	6	7	8	9	10	11	12	Total patients each dose
10 mg.	1	4	3	10	6	3	4	6	7	7	51
20 mg.			3	7	19	19	37	39	45	33	202
30 mg.						1	4	3	1	5	14
40 mg.						2	2	1	1	2	8
Total patients	1	4	6	17	25	25	47	49	54	47	275

doses as large as 30 mg. and 40 mg. daily, and these were all patients in the 8 to 12 yr. range. It may be well to keep in mind that these larger maintenance doses were employed after experience[3, 6] had given assurance that benzedrine® is relatively innocuous in children and that the severity of behavior problems necessitating referral to a psychiatric hospital encouraged strenuous treatment as long as it was within the realm of safety.

Table II indicates that, in general, dexedrine® was effective in definitely smaller doses than benzedrine®. Although the single most popular amount was 10 mg. daily, doses of 15 mg. and 20 mg. were employed relatively more frequently than were the larger amounts in the benzedrine® series. Small doses of 5 mg. of dexedrine® daily were found effective only in the younger children 3 to 7 yrs. of age, where amounts in excess of 10 mg. were rarely, if ever, used.

While a comparison of Tables I and II suggests that in general dexedrine® is effective, dose for dose, in approximately half the amount that is required for benzedrine®, it is obvious that there are likely to be exceptions to this in individual cases. Moreover, except at the extremes of lower age groups and largest doses, no strict correlations between age of child and most effective dose of either benzedrine® or dexedrine® are to be confidently expected.

Both drugs appeared to exert their effect upon behavior for periods of 6 to 10 hrs. after administration and, since both tended to interfere with sleep if given late in the day, the smaller amounts were given in a single dose each morning, either upon awakening or at breakfast time. With the larger doses of benzedrine® it frequently proved practical to order 20 mg. for the morning dose and the balance with the noon meal. With dexedrine® in the larger amounts 10 to 20 mg. in the morning and the balance at noon was frequently an effective method. The indications both for larger doses and an additional amount at noon were observations that for some children the effects of a morning dose tended to wear off early in the afternoon. It was frequently noted that during the period of the day when effects of either drug were waning there were temporary episodes of irritability, depression of mood or increase in motor activity. In an attempt to obviate this additional

TABLE II

NUMBER OF MALADJUSTED CHILDREN RECEIVING VARIOUS DAILY DOSES OF DEXEDRINE SULFATE ARRANGED IN GROUPS ACCORDING TO AGE

Daily dose	Age in yrs. 3	4	5	6	7	8	9	10	11	12	Total patients each dose
5 mg.	1	2		1	3						7
10 mg.		1		4	5	9	10	10	8	4	51
15 mg.				1	2	2	8	3	5	1	22
20 mg.					3	5	7	5	2	5	27
30 mg.						1	1	1	1	2	6
Total patients each age:	1	3		6	13	17	26	19	16	12	113

doses as late as 4:30 p.m. were tried. In some children receiving dexedrine® an afternoon dose of 5 mg. in addition to medication earlier in the day was tried. To a number of children listed in Table II as receiving dexedrine® 15 mg. daily the drug was given in 3 divided doses of 5 mg. each, the last in mid- or late afternoon. The tendency to insomnia that might be expected to follow such a regime appeared to be less frequent in most children than in adults, and often occurred only during the first few days of administration.

Behavior Changes

In the present series behavior changes of the types previously reported[3, 6] and described above were noted in response to dexedrine® as well as benzedrine®. Although many children reacted in a more dramatic manner to one of the drugs in contrast to what was noted with the other, there was little qualitative difference in the two situations as far as varieties of behavior change were concerned.

As reported in earlier communications (as noted above), the most frequent behavior response was that of more subdued behavior. This is best illustrated by quoting verbatim from the clinical record of a child who showed this particular reaction to benzedrine®:

Harold, aged 6½ yrs., was a seriously maladjusted boy who, both at home and for a considerable period of prior observation in the hospital, had been hyperactive, variable, quarrelsome, noisy and compulsive. From his hospital record it was noted that (starting a week previously) "the patient has been receiving benzedrine sulfate 20 mg. daily at 7 a.m. On the 1st day that he received it he complained of being sick to the stomach, lay down during the morning and was quiet and subdued. He slept for about half an hour late in the afternoon of that day. Since that time he has had no complaints. The medication brought about a dramatic change in behavior. Harold now goes about in a subdued fashion, is much more quiet than previously and is definitely less irritable. He looks serious, his attention span has greatly increased and he gets into much less difficulty with others in the group. Although he has spent but 1 day in school since receiving the medication it was noticeable that he was far less negativistic than previously and his attention span was longer and his interest better. Dining room behavior has distinctly improved."

Another type of response, which appeared neither so frequently nor so dramatically as the foregoing, was the appearance of stimulation of shy, recessive children to a more animated and successful participation in daily activities. This stimulated reaction is illustrated by another verbatim transcript from a clinical record:

Bill, an 8 yr. old boy, was under observation because at home and for several months in the hospital he had been extremely shy, always spoke in a low tone of voice, played by himself in preference to with others, and spent a good deal of time talking to himself. "This child received benzedrine sulfate 20 mg. daily before breakfast for 7 days. In the group he was a closer member with general improvement in social adjustment. He worked much harder in group activities and went swimming voluntarily each day. At school his program seemed to have been accelerated. He was more friendly and showed greater interest."

A small group of children showed improvement in school adjustment and accomplishment with benzedrine® or dexedrine® without, however, appearing to change in their general social adaptability in other situations. This type of improvement has been reported in detail elsewhere,[11] and is suggested in the remarks pertaining to school adjustment in the case reports included in the present communication. An increased "desire to work," "drive for accomplishment," "increase in attention span," "much better concentration," and "greater output of work" are frequent notes describing school improvement in the hospital notes. Such observations to the exclusion of better adjustment in other areas were apt to appear in the records of children where scholastic rather than general social problems were the foci of clinical atttention.

As may be expected in any clinical studies involving human response to specific drugs, a certain number of patients failed to show any demonstrable reaction to benzedrine® or dexedrine®.

In analyzing the specific behavior changes which did occur in response to treatment in the present study, Tables III and IV were prepared to show the proportion of all children treated who responded in 1 of the 4 ways described above. Since the actual number of patients involved in each of these and subsequent tables were not always identical, it seems wise to express results in terms of percentage of children treated in each tabulation.

The right hand vertical columns of Tables III and IV indicate the percentages of children responding to treatment by becoming subdued, by being stimulated, by improving in school only or by not being affected at all. The figures indicate that, with minor variations, the administration of either

TABLE III

BEHAVIOR RESPONSES AND THERAPEUTIC RESULTS IN 275 CHILDREN RECEIVING BENZEDRINE SULFATE

	Therapeutic result			Totals
	Improved	Unaffected	Worse	
Behavior response				
Subdued	58.9%	0	1.5%	60.4%
Stimulated	9.8%	0	9.8%	19.6%
Improved school performance alone	4.4%	0	0	4.4%
Unaffected	0	15.6%	0	15.6%
Totals:	73.1%	15.6%	11.3%	100.0%

benzedrine® or dexedrine® produced subdued behavior in 50 to 60% of the children, stimulation to greater activity in approximately 20%, improvement limited exclusively to the school situation in 5%, and no change worthy of note in 15 to 25%. These figures reflect what has been reported in earlier, though less comprehensive studies with benzedrine®,[3, 6] and may be accepted as an indication of the probability of the occurrence of specific behavior response in most maladjusted children. They also indicate that in terms of type of response there seems to be little choice between benzedrine® and dexedrine®.

Response in Terms of Therapeutic Value

In addition to the specific behavior evoked by a drug, responses may also be described in terms of their therapeutic value. Such an evaluation must always take into account the nature of symptoms requiring treatment. If an overactive, noisy child becomes more subdued as the result of receiving benzedrine® or dexedrine® he is considered to be improved. If the medication stimulates this same child to greater activity and accentuates his symptoms of maladjustment his condition may be considered worse. The same reasoning applies to other responses in other settings. It is obvious that therapeutic effect in this portion of the study is discussed at a symptomatic level and does not necessarily imply conclusions deeper than this level.

The bottom horizontal columns in Tables III and IV indicate the percentages of children symptomatically improved, unaffected or made worse by treatment with optimal doses of benzedrine® and dexedrine®, respectively. As in the case of figures for specific behavior responses, the results are rather similar for both drugs. They indicate that 60 to 75% of the children were improved by either drug, that 15 to 25% were unaffected and that 10 to 15% became worse. Closer study suggests that benzedrine® may have been a somewhat more favorable therapeutic agent, however, since 73.1% were improved through its use as contrasted to 61.1% with dexedrine®.

In correlating the figures in the vertical columns with those arranged horizontally in Tables III

TABLE IV

BEHAVIOR RESPONSES AND THERAPEUTIC RESULTS IN 113 CHILDREN RECEIVING DEXEDRINE SULFATE

	Therapeutic result			Totals
	Improved	Unaffected	Worse	
Behavior response				
Subdued	52.2%	0	1.8%	54.0%
Stimulated	5.4%	0	14.1%	19.5%
Improved school performance alone	3.5%	0	0	3.5%
Unaffected	0	23.0%	0	23.0%
Totals:	61.1%	23.0%	15.9%	100.0%

and IV it will be noted that the great majority of children considered improved by both drugs were those whose behavior became subdued. While the proportion who were thus benefited is impressive, the actual figures reflect the frequency with which hyperactivity is a major symptom in any group of maladjusted children. The apparent paradox that benzedrine® and dexedrine® help some children by producing subdued behavior and others by stimulating them to greater activity will be discussed later.

Therapeutic Value as Related to Clinical Diagnosis

Attempts to systematically evaluate special treatment in child psychiatry still suffer by the lack of a generally accepted, or even widely approved, classification of children's psychiatric disorders. However since some previous reports[6, 7] have referred to the value of benzedrine® as a therapeutic agent for certain special problems it seems worth while to discuss the relative merits of this drug and dexedrine® in such conditions as occurred in sufficient frequencies in the present series to warrant comparisons. Four different diagnoses were found describing at least 10 patients each in the group treated with both drugs and are accordingly presented for brief discussion.

Behavior disorders of psychogenic origin: This category was employed to include all children for whose problems the major etiologic factors appeared to involve emotional conflict. It covered by far the largest number of patients in both groups.

In the series of children treated with benzedrine® 157 patients were diagnosed as suffering from problems primarily of psychogenic origin. One hundred and eleven of these improved on benzedrine therapy, 24 were unchanged and 13 became worse. In terms of percentages these figures represent 70.3%, 21.5% and 8.2%, respectively.

There were 64 such patients in the dexedrine series of whom 37 (57.8%) were improved, 17 (26.5%) remained unaffected and 10 (15.7%) became worse during treatment.

The clinical effect of both drugs in this diagnostic group parallels the results obtained in the entire group of maladjusted children. The figures may be considered a rough index of the results to be expected when benzedrine® or dexedrine® are used with children suffering from the effects of emotional conflict.

Behavior problems associated with convulsive disorders: Behavior problems occurring in children who are having, or have had, repeated convulsions, or whose electroencephalographic patterns are definitely of one of the "epileptic" types make up the next largest group of children involved in this study. At the time of their treatment the behavior difficulties of these particular children overshadowed their seizures in clinical importance. Only those are included whose pharmacologic treatment at this time consisted solely of benzedrine® or dexedrine®.

There were 39 "convulsive" children who received benzedrine® of whom 30 (76.9%) showed improvement in behavior, 4 (10.3%) remaining unchanged and 5 (12.8%) becoming worse. In the dexedrine series there were 11 children so diagnosed of whom 5 (45.4%) were improved, 5 (45.4%) were unchanged and 1 (9.2%) became worse.

In disorders of this sort any improvement resulting from drugs which in themselves have minimal effect upon either electroencephalographic patterns or upon the seizures themselves is worthy of note. However, the discrepancy between extremely favorable results (76.9%) with benzedrine® and a much more modest volume of improvement (45.4%) with dexedrine® is conspicuous. This portion of the study suggests that benzedrine® is definitely the drug of first choice for behavior problems associated with convulsive disorders.

Psychopathic personality: This diagnosis is employed here to designate children whose problems appeared to arise from shallow and inconsistent emotional capacities resulting in repeated errors in judgment, failure to profit from experience, with both characterized by absence of evidences of serious or persistent inner emotional conflict. Such individuals are notoriously resistant to all therapeutic measures so that any favorable response to pharmacologic treatment is particularly impressive.

Of the children treated with benzedrine® 25 were classified as handicapped by psychopathic personality, of whom 21 (84%) showed improvement, 1 (4%) was unchanged and 3 (12%) became worse. Fourteen such patients received dexedrine® of whom 11 (78.6%) were improved, 2 (14.3%) were unchanged and 1 (7.1%) became worse. Both preparations seemed equally effectual and to a most gratifying degree in this resistant group.

Children with schizoid personality: Although schizophrenia is being diagnosed with increasing frequency by those who work with severely maladjusted children experience indicates that conservatism rather than enthusiasm should be the diagnostic keynote in this area. For purposes of the present

study it has seemed good judgment to classify children possibly falling into this group as characterized by schizoid personality, whether or not they were actually psychotic at the time. As in the preceding classification, such children are notoriously resistant to treatment, so that any favorable response to either drug may be considered encouraging.

In the benzedrine® series there were 22 children whose diagnosis was that of schizoid personality. Of these 14 (63.6%) were symptomatically improved during treatment, 3 (13.6%) were unaffected and 5 (22.8%) became worse. There were 14 schizoid children treated with dexedrine® of whom 7 (50%) responded favorably, 3 (21.4%) were unchanged and 4 (28.6%) became worse. While there seemed to be relatively little choice between the 2 drugs for this group, even temporary symptomatic improvement in 50 to 60% of schizoid children as the result of any therapeutic measure is worthy of attention.

Hypodermic Administration of Benzedrine®

All the observations so far recorded in this communication have dealt with children who received medication orally each day. In addition occasional opportunities presented themselves to study the responses of individual children who received benzedrine® in doses of 10 mg. and 20 mg. by hypodermic injection.

When given to children hypodermically benzedrine® produces its customary effects on mood and behavior within 5 to 15 min. The results are particularly dramatic when the effect is the rapid emergence of subdued, cooperative behavior in a youngster who has immediately prior to treatment been resistive, negativistic, noisy and destructive as illustrated in the following case report:

Muriel, an 11 yr. old girl of average intelligence, was admitted for psychiatric study because of persistent negativism to all training procedures, destructiveness of her own belongings and those of her foster parents and schoolmates, as well as repeated assaults upon younger children. She was passively cooperative to physical examination and other admission procedures over a 2 day period, including being confined to bed in a unit with 2 other children as part of the usual initial quarantine period. Her vaginal smear was then found to be positive for gonococcal infection, necessitating her remaining alone in the isolation unit after the others had left. On the morning that this was explained to her, she immediately became abusive to the nursing staff and destructive of her bed linen, and with much crying and profanity struggled to leave the confines of her bed and room. Bed restraints were applied but her noisy resistance continued without abatement for over 2 hrs. to the point of disturbing other activities in the building. Benzedrine sulfate 20 mg. was then administered hypodermically and a liberal supply of playthings placed within reach. In less than 10 min. Muriel became quiet and was shortly afterwards noted applying herself with intense interest to some coloring books and conversing pleasantly with the same nurse who had a short time before been the object of her profanity. Although she appeared pale and showed no appetite for her noon meal, she continued to keep herself busy and appeared quite content during the completion of arrangements for transfer to another hospital for the treatment of her infection.

Observations on Prolonged Administration

In a previous report[6] it was demonstrated that children receiving benzedrine® continuously for periods of 3 mos. and 6 mos. showed no evidence of developing tolerance to the drug and usually reverted promptly to their initial behavior patterns as soon as medication was discontinued. Resuming treatment after a few days' interval brought the same amelioration of symptoms noted over the previous several months. Observations during the present study confirmed these earlier results as far as benzedrine® was concerned and indicated that identical findings may be anticipated with the prolonged use of dexedrine®. Although no statistical data covering this portion of the studies is available, numerous random observations have indicated identical phenomena in a few children receiving each of the preparations for periods of as long as 2 yrs. One may anticipate in certain favorable instances permanently improved patterns of behavior as the result of prolonged successful adjustment and accomplishment during the pharmacologic treatment, particularly where the attitudes of others have been favorably influenced by the child's improvement. Although habituation to benzedrine® has been reported to occur in certain adult patients,[2] no such reactions were noted in any of the children observed in the controlled situation of the hospital during the entire 12 yr. period covered by this study.

Undesirable Effects and Complications

In approaching an ultimate analysis of the comparative merits of benzedrine® and dexedrine® as

therapeutic agents for maladjusted children, it is necessary to consider in some detail the undesirable effects of these drugs, insignificant as they may appear in the face of some of the dramatic effects described above. These may be considered both in terms of patients whose total adjustment became worse during treatment and those in whom isolated detrimental side effects were noted even when the total response was favorable.

Children whose total adjustment became worse: In Tables III and IV it will be noted that the behavior of 11.3% of the children became worse while they were receiving benzedrine® as compared to the same effect on 15.9% of those to whom dexedrine® was administered. The majority of those responding unfavorably did so by becoming stimulated to increased activity by the drugs, whereas less than 2% of all children treated were considered worse as the result of becoming too subdued. Where an increase in activity was considered unfavorable, common evidences of such a result were an exaggeration of all symptoms which had originally attracted clinical attention as well as evidences of increased tension, anxiety and agitation. Although the details varied with each patient, this type of response is illustrated in the following verbatim excerpt from one of the children's hospital records:

Herbert, aged 10 yrs., has been under clinical observation for some months because regardless of his surroundings he invariably chose to play by himself, occasionally cried aloud for no discernible reason and spent hours amusing himself by twirling small objects in his fingers while regarding them with an intense and rapt expression. He was considered to be suffering from a schizophrenic psychosis. It was noted that Herbert "received dexedrine sulfate 10 mg. daily at 7 a.m. for 7 days. He appeared agitated, talked more than usual and remained awake fairly late at night the first night or two he received this. In the outdoor program he appeared agitated and often threw himself down. He showed no interest in what was going on about him. For the next 7 days he received benzedrine sulfate 20 mg. daily at 7 a.m. and all the mannerisms which had been noted somewhat the week before became exaggerated. He appeared a great deal more worried and was often hyperactive and excited, particularly in the early morning and late evening. Appetite did not show much change from the previous week. After medication was discontinued he resumed his usual behavior."

Specific undesirable symptoms: In addition to the small group of children whose total adjustment became worse in the manner described above, there were a considerable number in whom specific undesirable symptoms appeared during treatment with both drugs. This rarely occurred in sufficient intensity to affect the general improvement in behavior, but may be temporarily distressing both to children and to those who are entrusted with their care.

It was a matter of common observation that most unfavorable side effects appeared only during the first few days on which either drug was employed, becoming less conspicuous or even disappearing as treatment continued.

Among the most frequent undesirable symptoms were decrease in appetite, often with associated gastrointestinal symptoms. These were sufficiently prominent as to merit a special study which will be discussed below. Insomnia was a not infrequent symptom at first but rarely proved a problem after a few days except in children who received some of their medication late in the day. Some children gave evidence of increased emotional tension by their set, drawn, "worried" facial expressions, or by accentuation of tic-like motor activities such as nail-biting, hair-pulling, nose-picking and the like. Some children became obviously ill at ease with evidences of poorly suppressed irritability, sometimes most conspicuous late in the day when the effects of medication seemed to be wearing off. Possibly correlated with this was the frequent observation that many children, to whom the medication was of dramatic assistance during the morning and early afternoon (often coinciding with school hours), became hyperactive and noisy by supper time and through the evening. Some patients reacted in part to the treatment by crying more frequently and easily, particularly during the first few days of therapy, as though the medication facilitated ease of emotional expression.

On a more strictly physiologic level evidences of peripheral vasoconstriction were a not unusual observation. This was frequently evidenced by pallor of the face, constriction of the superficial veins and coldness of the extremities. Such symptoms were most frequently seen for 3 or 4 hrs. immediately following medication and in some instances appeared exaggerated when benzedrine® was given hypodermically. A fine tremor of the extended hands often coincided with these symptoms.

Frequent periodic complete physical and laboratory examinations were carried out as a matter of good pediatric supervision on all children involved in the present study. No abnormalities in the area covered by these examinations were noted other than the occasional physical symptoms noted above.

In particular blood pressures and blood counts were not remarkable. This confirms the results of a more intensive study of these particular items noted in an earlier report.[3]

Appetite and gastrointestinal symptoms: The effects of benzedrine® and dexedrine® were especially studied in 28 children who received a variety of different doses of each drug for periods of 1 wk. each. It was noted that diminution in appetite was frequently apparent during the first few days of treatment with either drug in doses of 10 mg. and 20 mg. daily. Following at least 4 days of treatment significant decrease in appetite continued 4 times as frequently on daily doses of 20 mg. of benzedrine® as on 10 mg. or 20 mg. of dexedrine®.

Loss of appetite was occasionally accompanied by nausea or mild gastrointestinal distress. While with neither drug were these symptoms outstanding after the first few days of treatment they were more troublesome with benzedrine® and with dexedrine®, particularly when the former was given in amounts as large as 40 mg. daily.

TABLE V

COMPARATIVE EFFECTS OF OPTIMAL DOSES OF BENZEDRINE SULFATE AND DEXEDRINE SULFATE IN 82 CHILDREN WHO RECEIVED BOTH DRUGS

Best response on benzedrine ®	30
Best response on dexedrine ®	30
Equally favorable response to both drugs	7
Equally unfavorable response to both drugs	9
No response to either benzedrine ® or dexedrine ®	6
Total:	82

When each of the 28 children involved in this part of the study were questioned as to which preparation they preferred they usually chose "the yellow pills" (dexedrine®) because they were less apt to produce gastrointestinal discomfort.

Effect of prolonged use on children's weight: In view of the adverse effect of benzedrine® and dexedrine® on appetite, coupled with the fact that both have been recommended as adjuvants in treatments designed for weight reduction, their effect on the weights of children involved in the present study was specifically scrutinized in the case of 25 patients who were treated for periods longer than 3 consecutive months. It was noted that during the first few weeks of treatment many of these children dropped below the weight gain curve anticipated for growing children at their developmental level. These children customarily made up the slight deficit incurred as treatment continued and in the long run followed their anticipated normal increase in weight. Such weight loss as was noted occurred more frequently and to a greater degree in overweight and overnourished children as compared to those whose weights were average or below average at the time treatment was started. Where behavior became distinctly improved through the use of benzedrine® or dexedrine® it was rarely necessary to consider interrupting treatment because of disturbances in nutrition or growth.

Clinical Comparison of Benzedrine® and Dexedrine®

Most of the preceding observations have indicated to what extent certain reactions may be anticipated when benzedrine® or dexedrine® is administered to groups of maladjusted children. While most children respond favorably to both drugs, and in ways which were not dissimilar, experience in practice has indicated that any individual child will usually give a better response to one of the drugs than to the other. To further investigate this matter of individual preference the specific reactions to each drug of the 82 children who were treated with both were made the objects of a special study.

The comparative clinical effects of benzedrine® and dexedrine® on these children are roughly summarized in Table V. It will be noted therein that approximately one third of these patients gave their best individual response to benzedrine®, another third to dexedrine®, and the remainder were about equally divided in terms of responding equally favorably to both drugs, equally unfavorably to both, or of being apparently unaffected by either.

To further investigate this, Tables VI and VII were prepared showing the relative frequency with which certain specific behavior traits, both clinically desirable and undesirable, were evoked by each drug. It may be seen in Table VI that of 9 desirable traits the 1st 8 were noted more frequently during

TABLE VI

NUMBER OF CHILDREN SHOWING SPECIFIC FAVORABLE RESPONSES TO BENZEDRINE® OR DEXEDRINE ® IN 82 PATIENTS TREATED WITH BOTH DRUGS

Type of response	Benzedrine®	Dexedrine®
Quieter	33	27
Increased attention span	26	18
More cooperative	23	18
Kept busier	19	12
More ambitious	15	13
Neater care of belongings	13	9
More prompt	10	8
Improved personal appearance	6	5
Appeared happier	6	8

benzedrine therapy than with dexedrine®, though the numerical differences were in no instance large. Table VII indicates that of 6 undesirable changes resulting from medication, all but 1 were also more prevalent as the result of benzedrine®. However, in this group the particular characteristics of "more tense" and "striking decrease in appetite" were 2 to 3 times more frequent with this drug than with dexedrine®.

While the data in neither of Tables VI and VII give us the complete answer as to why, as shown in Table V, certain individual children find one drug clinically preferable to the other, it does suggest a clue. Apparently benzedrine® as compared to dexedrine® in the doses used in this study produces more striking effects, both favorable and unfavorable. It therefore becomes the drug of choice except where its unfavorable effects outweigh those which are clinically desirable as far as the total result is concerned. In the latter instance dexedrine® becomes preferable.

TABLE VII

NUMBER OF CHILDREN SHOWING SPECIFIC UNFAVORABLE RESPONSES TO BENZEDRINE® OR DEXEDRINE® IN 82 PATIENTS TREATED WITH BOTH DRUGS

Type of response	Benzedrine®	Dexedrine®
Striking decrease in appetite	30	12
More tense	27	15
More active early morning and evening	10	9
More seclusive	8	4
More active throughout the day	5	4
More irritable	14	19

Effect of Combining Sedatives with Benzedrine® and Dexedrine®

As has been already noted, many children receiving daily morning doses of benzedrine® or dexedrine® become overactive late in the day, apparently as the effects of the drugs wear off. Similar accentuated psychomotor activity may be noted in some children for a day or two after prolonged medication is abruptly terminated.

In systematic attempts to control the evening restlessness of children under treatment with benzedrine® and dexedrine® a variety of commercially available barbiturates of known rapid action and limited duration of effect were given, one at a time, in appropriate therapeutic dosage to a number of patients late each afternoon for several days. These preparations included sodium amytal® (sodium iso-amyl ethyl barbiturate), ipral calcium® (calcium ethyl isopropyl barbiturate), nembutal® (pento-barbital sodium), sodium alurate® (sodium allyl-isopropyl-barbiturate) and delvinal sodium® (sodium 5-ethyl-5 [1-methyl-1-butenyl] barbiturate). In most instances the administration of none of these barbiturates produced demonstrable effects on the hyperactivity and noisy restlessness of the children who received them. In numerous instances this type of accessory treatment appeared to stimu-

late the children to even greater motor agitation. As adjuncts to therapy with the amphetamines, the results did not encourage more extensive investigation or continued use.

Discussion

In general the preceding observations confirm what has already been reported as to the effect of benezedrine® on children's behavior. In view of the close chemical relationship between benzedrine® and dexedrine®, it is not surprising that their clinical effects are so similar. The implications for practical use of both drugs, based on the extensive experience herein reported, seem for the most part to be clear cut and self-evident.

In an earlier publication,[6] the suggestion was made that benzedrine® stimulates improved social adjustment in children by the sense of well-being which patients experience through its use. The irritations and conflicts which may be responsible for clinical symptoms either in the form of hyperactive, distractible or negativistic behavior on the one hand or passive, shy withdrawal on the other are apparently less distressing while medication is being given. As a result children return to a more "normal" adjustment, which for some appears to be more subdued behavior and for others stimulation to greater activity. The results of the present studies imply that benzedrine® and dexedrine® act similarly in this respect and that differences in behavior induced in various individual children by both drugs are not as paradoxic as they seem.

Habituation to benzedrine® by some adult patients has been reported[1] and at the present time there is a certain amount of public apprehension, based largely on misinformation,[24] that its use may lead to addiction. All reliable clinical evidence including the observations reported above indicate that benzedrine® and dexedrine® have an unusually wide range of safety and are not true habit-forming drugs. However, the use of both preparations may be accompanied by a reduction in appetite and other mild but annoying symptoms, as well as, in a small proportion of children, accentuation rather than relief of behavior symptoms. These considerations suggest that benzedrine® and dexedrine® are not to be used indiscriminately for every behavior problem encountered in the physician's practice. However, when employed judiciously following the procedure and indications implied in results of the present study, they may bring prompt and dramatic symptomatic relief to many children suffering from severe and otherwise discouraging disabilities.

Summary

The effect of benzedrine® (dl-amphetamine) and dexedrine® (d-amphetamine) sulfates upon the behavior of maladjusted children was studied in the somewhat controlled setting of a children's psychiatric hospital. Twelve years' experience with these drugs is reported involving observations upon 275 children who received benzedrine®, 113 who received dexedrine® and 82 who received both preparations.

The most frequent optimal daily dose was 20 mg. of benzedrine® and 10 mg. of dexedrine®.

Specific behavior responses to both drugs approximated one another both in quality and frequency, with 50 to 60% of the children becoming more subdued, 15 to 25% showing no change, 20% showing increased activity and 5% showing an acceleration of school progress only. Clinically these reactions indicated 60 to 75% symptomatic improvement, 15 to 25% no change and 10 to 15% unfavorable responses. Children with a variety of clinical diagnoses were benefited with no evidence of tolerance or addiction following prolonged administration.

Occasional undesirable physiologic side effects were noted with both preparations, most frequently during the first few days of treatment only. Approximately equal numbers of children responded more favorably to one drug in contrast to the other. In general benzedrine® was found to produce the more dramatic results, except with individual children in whom its side effects were more pronounced, in which cases dexedrine® proved more advantageous.

The conclusion is drawn that these drugs influence children's behavior by altering their emotional reactions to distressing situations. Both offer the practitioner readily available and easily controlled pharmacologic approaches to the symptomatic treatment of children's behavior disorders.

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SPANISH ABSTRACT

Benzedrina® y Dexedrina® en el Tratamiento de Desordenes de Comportamiento de Niños

El efecto de los sulfatos de benzedrina (dl-amfetamina) y dexedrina (d-amfetamina) en el comportamiento de niños desconformes fué estudiado en el ambiente algo controlado de un hospital psiquiatrico de niños. Se informa que una experiencia de doce años con estas drogas comprende observaciones hechas de 275 niños que recibieron benzedrina®, 113 recibieron dexedrina® y 82 que recibieron ambas preparaciones.

La dosis diaria optima más frecuente fué benzedrina® 20 mg. y dexedrina® 10 mg.

Las respuestas de comportamiento específicas a ambas drogas se aproximaban una a otra en calidad y frecuencia, volviendos el 50 o 60% de los niños suminos, 15 a 20% no mostraron ningún cambio, 20% mostraron más actividad y 5% mostraron solamente una aceleración en el progreso escolar. Clinicamente estas reacciones indicaron 60 a 75% progreso sintomático, 15 a 25% ningún cambio y 10 a 15% respuestas desfavorables. Niños con una variedad de diagnosis clínica beneficiaron sin ninguna prueba de tolerancia o adición después de administración prolongada.

Se notaron de vez en cuando efectos del lado psicológico poco deseables con ambas preparaciones, más frecuentemente durante los primeros pocos días de tratamiento solamente. Aproximadamente el mismo número de niños respondió más favorablemente a una droga en contraste con la otra. En general, se encontró que la benzedrina® produce resultados más dramáticos, excepto en niños individuales en quienes sus efectos fueron más pronunciados, en cuyos casos la dexedrina® fué más ventajosa.

Se llegó a la conclusion de que estas drogas influencian el comportamiento de los niños alterando sus reacciones impresionables en situaciones desesperantes. Ambas ofrecen al practicante un acercamiento farmacológico facilmente disponible y controlado para el tratamiento sintomàtico de los desordenes de comportamiento de niños.

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PASSIVE INTRAPERITONEAL MOUSE PROTECTION TEST IN A STUDY OF IMMUNE RESPONSE TO H. PERTUSSIS VACCINATION

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THIS investigation was undertaken to evaluate the anti-H. pertussis mouse protection test as a method of determining the effectiveness of immunizing young infants (3 to 7 months of age) against pertussis and to compare the values determined by this method with titers obtained by a rapid pertussis agglutination test.

EXPERIMENT I

Method

Thirteen infants, aged 3 to 7 mos., having no history of or exposure to clinical pertussis, were given 3 subcutaneous inoculations of phase I pertussis vaccine* containing 20 billion organisms/ml. The injections were given in the deltoid region at approximately 2 wk. intervals in doses of 1 ml., 2 ml. and 2 ml.

Blood samples of 5 ml. were drawn before immunization and whenever possible 2 wks. to 5 mos. after immunization. The sera were maintained in the frozen state until tested.

Cultures of H. pertussis, freshly isolated from a proved case of pertussis, were lyophilized after 2 transplants on a modified Bordet-Gengou medium containing 35% defibrinated human blood.

The gastric mucin (hog), which was used to enhance the virulence of the challenging organisms, was prepared in the following manner: 10 gm. of granular hog mucin (Stock 1701 from Wilson and Company, Chicago, Ill.) was added to 185 ml. of water, thoroughly mixed and autoclaved. The resulting suspension was centrifuged at low speed for 4 min. and the viscid supernate reclaimed and adjusted to pH 7.0-7.2.

The technic of the mouse protection test was similar to that used by Mishulow.[1] The tubes of lyophilized H. pertussis were opened aseptically, the contents suspended in 0.4 ml. beef extract broth and slants of freshly prepared moist Bordet-Gengou medium inoculated. A heavy growth of typical phase I organisms was obtained in 48 hrs. and, after 3 successive transplants at 24 hr. intervals, the culture was checked for purity and phase I characteristics. The organisms which were removed carefully so as not to include medium were emulsified in sufficient Ringer's solution to give a turbidity of approximately 10 billion organisms/ml. The bacterial emulsion then was mixed thoroughly with sufficient hog mucin solution to give a calculated dose of 500 million organisms/ml. of mixture (an amount, determined by preliminary experiments, sufficient to kill approximately 60 to 80% of inoculated mice). The bacterial suspension and the diluent were kept at 37° C. before and during testing.

A group of 8 to 10 white inbred Swiss mice, 14 to 17 gm. in wt., was used to test each sample of serum. Pertussis Human Immune Serum obtained from the Philadelphia Serum Exchange was used in 1 test group. The mice were injected with 0.2 ml. of serum into the muscles of the leg and 2 hrs. later were challenged with 1 ml. of the bacterial suspension intraperitoneally. At this time, 2 control groups of 7 and 10 mice also received the challenge dose.

The remaining portion of each serum was tested by the rapid pertussis agglutination test devised

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* Supplied by Eli Lilly and Company. This vaccine contained, in addition to the whole organisms, the products of metabolism as obtained from the washed medium.

TABLE I

MORTALITY IN CONTROL GROUPS AND IN GROUP OF MICE THAT RECEIVED PERTUSSIS IMMUNE SERUM

	Agglutination	Mice Tested	Mice Tested Died—Days										
			1	2	3	4	5	6	7	8	9	10	Total
Pertussis Immune Serum	S.P.*	9	1	0	0	0	0	0	0	0	0	0	1
Control Group I		10	1	3	2	0	1	0	0	0	0	0	7
Control Group II		7	0	1	4	0	1	0	0	0	0	0	6

Per Cent Mortality (Control Groups) = 76.5

* S.P.—Strongly positive.

by Powell and Jamieson.[2] This test was conducted by adding a small drop of blue pertussis antigen (colored with methylene blue) to a drop of serum on a piece of glazed waterproof cardboard. The combined drop was stirred a few seconds and the card then rocked back and forth for about 1 min. If the serum contains appreciable antipertussis agglutinating antibody, the process of ensuing agglutination can be seen as granulation and clumping of the blue-colored antigen. "Weakly positive" rapid test results correspond to test tube titers of 1:10 to 1:20; "strongly positive" rapid test results correspond to test tube titers of 1:40 or over.

Agglutination tests on each serum were carried out and read separately by the author and an assistant as it had been learned from preliminary observations that the test is subject to some variation in interpretation.

TABLE II

SUMMARY OF RESULTS WITH PREIMMUNIZATION SERUM

Subject	Age in Mos.	Agglutination	Mice Tested	Mice Tested Died—Days										
				1	2	3	4	5	6	7	8	9	10	Total
I	5	W.P.*	10	5	0	0	0	0	1	0	0	0	0	6
II	5	N†	10	2	2	1	1	1	0	0	0	0	0	7
III	6	N	10	2	3	1	0	0	0	0	0	0	0	6
IV	5	N	10	0	2	3	1	1	0	0	0	0	0	7
V	7	N	8	1	4	1	0	0	0	0	0	0	0	6
Totals			48											32

Per Cent Mortality, $p^1 = 66.7$

* W.P.—Weakly positive.
† N—Negative reaction.

Results

All mice were observed for 10 days and it was noted that none died after the 6th day. The data are summarized in Tables I, II and III. In Table I, it can be seen that 13 of the 17 control mice (76.5%) died within the 6 day period. One of the 9 mice receiving the Pertussis Immune Serum (Human) died and the agglutination of this serum was strongly positive (S.P.).

The average per cent mortality of the control group was 76.5 and the average per cent mortality of the groups of mice treated with serum from the subjects before immunization was attempted was 66.7

TABLE III

SUMMARY OF RESULTS WITH POSTIMMUNIZATION SERUM

Subject	Age in Mos.	Serum Obt'd. Wks. After Immunization	Agglutination	Mice Tested	Mice Tested Died—Days										
					1	2	3	4	5	6	7	8	9	10	Total
IV	6	17	S.P.*	9	0	3	0	0	0	0	0	0	0	0	3
V	5	2	S.P.	10	1	2	0	0	0	0	0	0	0	0	3
VI	4½	2	W.P.	9	2	0	0	0	0	0	0	0	0	0	2
VII	5½	2	W.P.	10	1	1	0	0	0	0	0	0	0	0	2
VIII	5	13	W.P.	10	1	0	0	0	0	0	0	0	0	0	1
IX	6	3	W.P.	10	1	0	0	0	0	0	0	0	0	0	1
X	4	8	W.P.	10	0	0	0	0	0	0	0	0	0	0	0
XI	5	4	W.P.	10	0	0	0	0	0	0	0	0	0	0	0
XII	3	17	N	10	0	1	0	0	0	0	0	0	0	0	1
XIII	7	13	N	10	0	2	0	0	0	0	0	0	0	0	2
Totals				98											15

Per Cent Mortality, $p^2 = 15.3$

$$\frac{p_1 - p_2}{\sigma_{p_1 - p_2}} = \frac{51.4}{8.22} = 6.25$$

* S.P.—Strongly positive.

(Table II). This difference can be attributed to chance variation and is not statistically significant.

The postimmunization sera gave significantly good to excellent protection (Tables II and III). The calculations show that the difference between the 2 percentages (51.4) is highly significant.

In most cases the agglutinin titers did not show close correlation with values obtained by the mouse protection test (Table III). The protective value of a serum apparently was not greatly influenced by the age of the infant at the time immunization was started, nor was it influenced by the time elapsing before withdrawal of blood (within 2 wk. to 5 mo. period) after completion of immunization.

TABLE IV

CONTROL GROUP

	Mice Tested	No. Dead in 10 Days
Control Group I	10	7
Control Group II	10	7
Preimmunization Serum Tested Group	10	7

Per Cent Mortality, $p^1 = 70$

EXPERIMENT II

The method was the same as in Experiment I with the exception that the challenging dose of organisms was given 19 to 20 hrs. instead of 2 hrs. after the serum injection. It was thought that this change in procedure would enhance the accuracy of the test since it allowed more time for the experimenter to make the preparations and injections. The sera from 10 children were tested in 100 mice; results are summarized in Tables IV and V.

None of the mice died after the 5th day and although all mice were observed for 10 days, all test and control mice which survived the 5th day appeared well. Seventy per cent of the control mice died within 5 days after injection. Although the per cent fatality among the groups of mice treated with the postimmunization sera varied more than in Experiment I, the per cent fatality of the treated mice

TABLE V

SUMMARY OF RESULTS WITH POSTIMMUNIZATION SERUM

Subject	Age in Mos.	Serum Obtained—Wks. After Immunization	Agglutination	Mice Tested	Mice Tested Died—Days
XIV	4½	20	S.P.	10	5
XV	6	5	S.P.	10	2
XVI	6	16	S.P.	10	1
XVII	4	13	S.P.	10	1
XVIII	4½	4	S.P.	10	1
XIX	5	6	W.P.	10	3
XX	5	3	W.P.	10	3
XXI	5	4	W.P.	10	2
XXII	4	2	N	10	2
Totals				90	20

Per Cent Mortality, $p^2 = 22.2$

$$\frac{p_1 - p_2}{\sigma_{p_1 - p_2}} = \frac{47.8}{10} = 4.78$$

TABLE VI

CONTROL GROUP

	Mice Tested	No. Dead in 10 Days
Control Group I	10	10
Control Group II	10	10

varied significantly from that of the control and preimmunization serum tested groups. The calculations are shown in Table V. In this series, the results of Experiment I are substantiated further.

Although the case fatality in Experiment II was slightly higher (22.2%) than in the mice which received the challenge dose 2 hrs. after serum treatment (15.3%), the difference is not statistically significant.

EXPERIMENT III

The method was the same as in Experiment II with the exception that the weight of the mice and the challenge dose of organisms were modified to produce an approximate 100% mortality in the control mice. This required the use of mice weighing 12 to 14 gm. with an intraperitoneal challenging dose of 1 billion organisms suspended in the mucin solution. The data are tabulated in Tables VI and VII.

In the control group all the mice died within 3 days. In this experiment the 8 groups of 10 mice had a mortality of 62.5% which is significantly different from that of the control group.

DISCUSSION

The data obtained by the passive intraperitoneal mouse protection test as performed indicate that significant protection is given by small amounts of serum from infants immunized with a phase I H. pertussis vaccine. These protective antibodies apparently did not exist in the sera of young children who had not been exposed to pertussis.

TABLE VII

SUMMARY OF RESULTS WITH POSTIMMUNIZATION SERUM

Subject	Age in Mos.	Serum Obtained—Wks. After Immunization	Agglutination	No. of Mice	No. of Mice Dead in 10 Days	Per Cent Deaths
XXIII	4	20	S.P.	10	7	70
XXIV	5	4	S.P.	10	5	50
XXV	6½	9	W.P.	10	8	80
XXVI	4½	12	W.P.	10	7	70
XXVII	5½	3	W.P.	10	6	60
XXVIII	5	11	W.P.	10	5	50
XXIX	4	12	W.P.	10	4	40
XXX	4	7	N	10	8	80
Totals				80	50	62.5

Agglutination values did not correlate closely with the degree of protection, a fact that has been noted previously by Mishulow,[1, 3] with sera obtained from active and recovering cases of whooping cough. The agglutination response in postimmunization sera varied considerably, there being 9 strongly positive, 14 weakly positive and 4 negative reactions with 27 samples. The elapsed time (two weeks to five months) between the immunization of the subject and the drawing of serum had no demonstrable effect on the mouse protective value of the serum.

Although the number of children immunized was small, it is of major interest to note that protective antibodies were produced in children who were immunized at the age of 3 to 6 months and that the protective values at 3 and 4 months were as high as those in children immunized at 5 and 6 months of age. This would give further evidence to recent studies,[4-8] using other methods, that a large proportion of young infants can respond to immunization with H. pertussis.

Mishulow has shown that protective antibodies develop consistently after clinical pertussis and that agglutinating and complement-fixing antibodies do not.[3] Therefore, the demonstration of protective antibodies after vaccination promises to provide a reliable method of evaluating the efficacy of vaccination, providing that further tests will show that infants who possess mouse protective antibodies are resistant to the disease. Such a method also could be used as a means of testing vaccine potency in the human subject. The intracerebral route for the challenging dose of organisms following active immunization of test mice, however, seems a more satisfactory test for vaccine potency.[9]

There are technical difficulties inherent in the passive intraperitoneal mouse protection test. A primary disadvantage is the relatively large quantity of serum to be obtained from the infant. No practical method of obtaining capillary blood will give sufficient quantities and, in most cases, it is necessary to resort to jugular or femoral punctures. Another difficulty lies in the variation in the challenge dose of organisms required to produce a sufficiently high death rate in mice injected by the intraperitoneal route.[10] The variations may be explained by such factors as the "age-weight" relationship,[11] strain variation in mouse resistance, and the variability in virulence of different strains of H. pertussis.[9] The test appeared to be more sensitive in Experiments I and II in which the smaller intraperitoneal challenging doses were used.

Summary

A passive mouse protection test and its use in testing sera from infants given a course of phase I pertussis vaccine is described. Infants 3 to 6 months of age consistently developed mouse protective antibodies following immunization with a phase I H. pertussis vaccine. Agglutinating antibodies did not develop consistently in these infants and the agglutinin titer did not closely parallel the values obtained by the mouse protection test.

Acknowledgment

The author wishes to express appreciation to Dr. Hilda Pope, Department of Bacteriology, and to Dr. John Erickson, formerly of the Department of Biochemistry, Duke University School of Medicine, Duke Hospital, Durham, N.C.

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SPANISH ABSTRACT

Ensayo de Protección Ratón Intraperitoneal Pasivo en el Estudio de Respuesta Inmune a la Vacuna H. Pertussis

Se describe un ensayo de protección ratón en su uso en el análisis de suero de infantes a quienes se les ha dado un curso de vacuna pertussis Fase I. Infantes de 3 a 6 meses de edad conformemente desarrollaron anticuerpos protectores de ratón después de la inmunicación con una vacuna pertussis Fase I H. Los anticuerpos aglutinantes no se desarrollaron conformemente en estos infantes y el título de aglutinina no correlacionó mucho con los valores obenidos mediante el ensayo de protección de ratón.

Duke University School of Medicine

LOUISIANA'S PROGRAM FOR THE CARE OF THE PREMATURE INFANT

By SIDNEY S. CHIPMAN, M.D., M.P.H., AND WALDO L. TREUTING, M.D., M.P.H.
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A WEIGHT of 2.5 kg. or less was recorded on approximately 5% of the 74,872 birth certificates filed in 1947 in Louisiana where nonwhites comprise 36% of the population and produce 37% of the births. There were 923 deaths ascribed to prematurity, implying a case fatality rate of 25%. Since the tendency of the Negro race in the United States to produce smaller offspring is well established, a nonwhite infant of 2500 gm. is likely to be more mature than a white infant of corresponding weight and should therefore have a better chance of survival. In view of our large nonwhite population, one would expect our over-all experience to be more favorable than that of states where this situation does not exist.

ESSENTIAL CHARACTERISTICS OF A PROGRAM

The component parts of a program for the care of the premature may well be restated even though you may be familiar with them. Case finding, both through prenatal care and by prompt reporting of premature births, is the first essential. Placement in a properly equipped hospital in which medical and nursing care of a high quality is available is desirable. Investigation of the home and follow-up of the infant is a necessary part of any program. Training and supply of personnel skilled in the care of these infants are of paramount importance. To these must be added cooperation and integration of effort between physicians, public health personnel and social service agencies.

THE PROGRAM IN LOUISIANA

A. Case Finding: This phase of our program is still largely in the blueprint stage. It has not received as much attention as it might because an unusually large number of obstetric cases at the state hospitals has kept all the existing facilities for the care of the premature infants completely occupied. Efforts should and will be directed towards obtaining the cooperation of all physicians and other attendants in the prompt reporting of premature births.

B. Placement: Since the premature's chances of survival are usually better in the hospital, it seems logical to deal with this phase of the problem first. The map in Chart 1 illustrates the location of the seven general hospitals in the state hospital system. Locations are well distributed but a trip of 50 to 100 miles to the nearest hospital may still be necessary. Facilities for the care of premature infants in these hospitals are grossly inadequate, except in New Orleans, but the other hospitals will serve as a nucleus

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in the development of more adequate care. It is evident that the unit at the Charity Hospital in New Orleans is and probably will remain the center of the entire program and it is with this hospital that we have had major concern until the present time.

The New Orleans Charity Hospital is one of the largest general hospitals in the country and is the teaching hospital for the medical schools of Louisiana State and Tulane Universities. Medical service in the premature unit is provided by the

CHART 1. Charity hospital system, State of Louisiana.

pediatrics staffs of the two schools and a smaller independent service. Such an arrangement has many advantages but it makes planning more difficult and time consuming. Cordial cooperation has always been present. Dr. Chester A. Stewart, prior to his death, and Dr. Ralph V. Platou and Dr. Myron E. Wegman, since, have rendered yeoman service in the development of the project.

The Charity Hospital in New Orleans, constructed in 1938, provides equal facilities for white and nonwhite patients in all departments. The recent tremendous increase in the number of hospital deliveries in the nonwhite group was not anticipated and facilities on the nonwhite obstetric and newborn services have been seriously overcrowded. The increase at Charity Hospital has been accentuated by the existence of only one other hospital in the city admitting these patients. In 1947 in this hospital there were 8983 live births of which 82% were nonwhite. The technical difficulties in providing adequate care for such a large number of newborns can readily be appreciated. During

the same year there were 750 admissions to the premature unit of which 694 or 92.5% were nonwhite. The problem in this hospital then is essentially one of providing facilities and care for an extraordinarily large number of prematures. Many of the difficulties can be attributed to "the curse of bigness," to use the words of the late Mr. Justice Brandeis. The daily census in 1947 was often over 90 and reached a high of 96. (In September 1948 it reached 105.) Provision of facilities for such a number of prematures in one institution has not been attempted elsewhere, to our knowledge. Because of the magnitude of the problem, it has been our general practice to limit

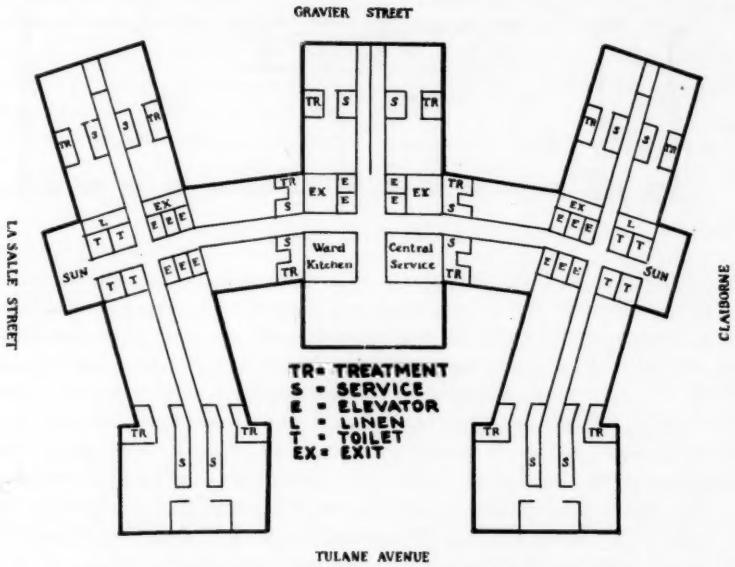

CHART 2. Typical general floor plan, Charity Hospital, New Orleans.

admissions to infants whose birth weight is less than 2250 gm. and selected infants whose weight is in excess of that figure.

When the hospital was planned no separate provision was made for premature infants. White prematures were cared for in the newborn nurseries. The Negro prematures were kept in one of the pediatric wards. Interest in improving this situation dates back to 1941 when a study revealed that the mortality among prematures was over 50%. Shortly thereafter the hospital enlisted the interest and support of the State Department of Health and the Children's Bureau. The central wing of the pediatric floor was set aside for premature infants, incubators and other special equipment purchased, and provision made for increasing the humidity of the atmosphere in these wards. Chart 2 illustrates the facilities in existence at that time. Your attention is drawn to the large wards on either side of a central partition. Each of the four large wards was capable of accommodating 30 to 40 infants but one of these was used as a classroom. There was considerable wasted space in the corridors and storage and workrooms were inadequate in number.

The problem of constructing an enlarged modern unit from such existing facilities was not an easy one. Much cooperative planning on the part of the hospital, the

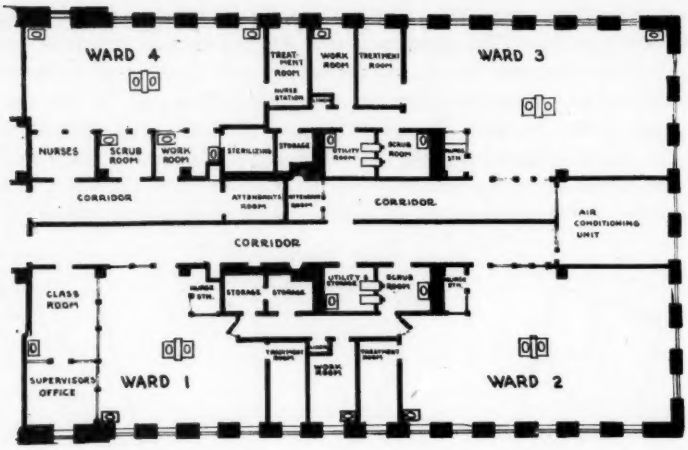

CHART 3. Premature unit, Charity Hospital, New Orleans.

pediatric staffs and the State Department of Health with the Children's Bureau has been necessary. Expense for reconstruction and equipment has been considerable and has been shared by the hospital and governmental agencies. The desirability of creating several smaller wards was recognized but it was felt that the expense involved did not warrant it. Futhermore, separate smaller units would have increased the ever-present difficulty of providing sufficient nursing service. Chart 3 shows the present arrangement, similar in general to the unit in 1946 but with the addition of new treatment rooms, additional storage and sterilization facilities and more wash basins. The entire unit has been air-conditioned and new lighting installed. Table I gives the pertinent data concerning the nurseries in terms of their size, the number of infants in each nursery and the amount of floor space per infant.

Establishment of criteria for assignment to the various wards has been a knotty problem. We have discarded the use of the more commonly accepted terms "clean" and "suspect wards" feeling that, where there are only two large wards to deal with, the moving of an infant under suspicion of harboring a communicable disease serves little purpose and may possibly contaminate both wards. Furthermore, it has been our impression that infections have appeared just as frequently in the ward designated as "clean." This raises the question as to whether the designation "clean" may promote

TABLE I

DESCRIPTION OF NURSERIES

Nursery No.	Floor space in. sq. ft.	No. of infants	Sq. ft. of floor space per infant
1 (graduate)	750	20	37
2	1292	35	37
3	1292	35	37
4 (isolation)	774	15	52

false confidence and result in less careful adherence to accepted technics of nursing care. At the present time we are continuing the custom of admitting infants born within the hospital delivery rooms to Ward 2 and those born elsewhere to Ward 3, but the same standards of nursing technic and time have been established for both groups. Those nearly ready for discharge, and thus requiring less nursing care, are transferred to Ward 1.

It has been suggested that the principle of separation by weight might be extended to the differentiation between Wards 2 and 3. By grouping in one ward all the smallest infants who are more vulnerable, one would facilitate the allocation of more nursing time to these infants. Since inadequate nursing care, qualitatively and quantitatively, is one of the major factors in the spread of infection among premature infants, the separation by weight may be more effective in preventing spread than segregation according to possible prior contamination.

Ward 4, previously used as a classroom, is reserved for infants with a communicable disease. It would have been more desirable to have placed this ward in another part of the hospital, but, since this was impossible, it has been set up as a complete "unit within the unit," entirely separate as to equipment and nursing staff, and with no direct communication to the rest of the unit. Additional space has been allowed each infant in this ward so as to minimize the possibility of cross infection; a more liberal allotment of nursing time per infant has been arranged.

Due to the shortage of trained nurses it has been necessary to employ ward maids to perform certain specified duties. These subprofessional workers, in most instances, have obtained all their training and experience in the premature wards. Considerable care has been exercised in original selection and a graded training program arranged for all. Under supervision, selected maids start with the cleaning of the floors and equipment and progress to the handling of linen and supplies and ultimately to the diapering and feeding of infants. Duties and responsibilities vary according to ability and training; those with demonstrated ability feed normal infants. Our experience has been highly satisfactory and it is felt that carefully selected and trained help of this type can render care of a high quality and is of inestimable value.

C. Follow-up: Follow-up starts soon after delivery with the education of the mother in the care of the infant. Instruction, including demonstrations, given by the public health nurse in the home, must follow and conform to that initiated by the hospital nurses. The importance of adequate provision for follow-up visits cannot be over-emphasized. New Orleans, a city of 600,000 persons, is unique in that a majority of all births in the city and 25% of all nonwhite births in the state take place within this hospital. Thus a referral system is relatively easy to arrange. A messenger from the city health department visits the hospital each morning to pick up referral slips which have been prepared by the nursing staff. This service includes all newborn infants—full term and premature. Since the former usually remain in the hospital only 36 to 72 hours referrals are made at the time of discharge.

Follow-up for prematures is handled as follows: A. A few days after the birth of the infant, at which time the mother usually is at home, a visit is made by the public health nurse to determine the facilities at home and to make suggestions regarding plans for the care of the infant. The results of this visit are reported to the unit in the hospital. B. The home situation is re-investigated just prior to the infant's discharge from the hospital. C. A third visit is made following the infant's discharge to ascertain

its early progress and to help with the early difficulties frequently encountered.

Due to the continuing shortage of public health nurses, this schedule is not always completed and the second of the visits is frequently omitted.

No attempt has been made at an evaluation of the accomplishments of this plan of public health nursing follow-up but there can be little doubt that the home instruction and supervision have been fruitful. There may, of course, be some question, from the standpoint of budgeting of total available nurse's time, as to what proportion should properly be devoted to premature infants, who at the time of discharge should be at least as vigorous as normal newborns.

Health supervision of premature infants, except for a small group under special study, is carried out at the child health stations of the city health department rather than in the outpatient departments of the hospital. This plan is in part based on the thought that in this way the infants will have less exposure to infections. Follow-up of infants whose home is outside the city has not been as well organized but a similar plan of procedure for referral to local health units is being developed.

D. Training Program: The potential value of this premature unit as a training center was one of the reasons for its establishment. A personnel training program must provide for both nurses and physicians and is the joint responsibility of the pediatric staffs of the medical schools and the department of nursing education of the hospital. The Children's Bureau, through the State Department of Health, is helping to support the educational phases of the project although actual instruction and over-all supervision are in the hands of the hospital authorities.

The training program for nurses was delayed by the difficulty in obtaining an educational director with the qualifications and experience essential to such a program. It is hoped that before too long there will be at the unit at all times 5 to 10 graduate nurses receiving theoretic and practical advanced training. Thus equipped, they will be available for extension of the program elsewhere in the state.

The problem of training physicians is complicated by the desire to restrict the number of individuals entering the wards and thus to limit the potential sources of infection. There are three residents working in the premature unit for a two month period and most of these men will return later in their training for a second period. As a source of case material and for demonstrations, the unit is of great value in the instruction of both undergraduate and postgraduate students. Consideration is being given to the feasibility of arranging for physicians, singly or in small groups, to observe the unit in operation.

The existing postgraduate programs of the two medical schools and the State Departments of Health in Louisiana and Mississippi should be of great value in carrying the educational program regarding premature infants to a wide area of the South.

Summary

Louisiana's program for the care of the premature infant has been discussed in terms of the need for such a program and of its component parts.

Little effort has been directed towards expansion of case finding since all facilities available for the care of the prematures are already overtaxed.

Hospital placement at the present time centers around the unit constructed in the Charity Hospital in New Orleans, where facilities have been planned to accommodate 80 to 100 infants. Because of the large numbers involved many problems have arisen regarding construction and organization.

A system of home investigation and follow-up has been well developed in the New Orleans area.

Plans for the training of nurses and physicians in the care of the premature are complicated by the need for minimizing the number of contacts with these infants. Members of the house staff and undergraduate nurses participate in the activities of the unit. Courses for graduate nurses will begin shortly and a more comprehensive training progam will be developed.

SPANISH ABSTRACT

El Programa de Louisiana para el Cuidado del Infante Prematuro

Las estadisticas de Louisiana muestran que un gran número de infantes nacen prematuramente y que la proporción de muerte entre estos infantes es alta. El programa de Louisiana para el cuidado de prematuros se concentra alrededor del Charity Hospital en Nueva Orleans y es el resultado de esfuerzos cooperativos combinados del hospital, los departamentos de salubridad del estado y de la ciudad, el "Children's Bureau" y las dos escuelas de medicina en la ciudad.

La gran unidad prematura en el hospital ha sido reconstruída y se ha dividido en cuatro cunas grandes con aire acondicionado en las cuales hay suficiente espacio para cada infante. Una sala cuna se usa para el cuidado de infantes mayores y otra, funcionalmente separada de las otras, se dedica al cuidado de aquellos infantes con enfermedades contagiosas. Todos los otros infantes prematuros son admitidos en una de las dos salascuna que quedan.

Se ha reconocido que un programa comprensivo para el cuidado de infantes que han nacido prematuramente debe incluir investigación de casos, colocación en hospital, entrenamiento de personal, investigación de hogar y vigilancia. Hasta la fecha, se ha puesto gran énfasis en este estado en la organización de un centro de entrenamiento para que el personal hábil quede disponible a ayudar en el desarrollo de otras fases del programa en todas las regiones del estado.

Louisiana State University School of Medicine

OBSERVATIONS ON ACUTE LEUKEMIA IN CHILDREN TREATED WITH 4-AMINOPTEROYLGLUTAMIC ACID

By STEPHEN D. MILLS, M.D., J. M. STICKNEY, M.D., AND ALBERT B. HAGEDORN, M.D.
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THE RECENT publications of Farber and co-workers[1, 2] dealing with the treatment of acute leukemia in children have awakened widespread interest. Their investigations have stimulated hope for the amelioration of symptoms of this fatal disease and indicated the possibility of provoking remissions that lengthen the lives of those patients affected by it, while making them more comfortable at the same time.

In investigating leukemia and allied conditions of a neoplastic nature, Farber and co-workers noted what they termed an "acceleration phenomenon" in the blood and bone marrow of leukemic children treated with folic acid or its conjugates such as diopterin (pteroyldiglutamic acid) or teropterin (pteroyltriglutamic acid). There was marked hyperplasia of the marrow as well as of other sites of leukemic involvement at postmortem examination. They reasoned that if folic acid or its conjugates speeded up the leukemic process, an antagonist to folic acid might be devised in order to retard the progress of the disease or stop it altogether. Through co-operation with the research division of one of the major pharmaceutical firms, a series of folic acid antagonists was soon developed. One of these was aminopterin (4-aminopteroylglutamic acid). It differs from folic acid only in the substitution of the NH_2 group for the OH radical in the fourth position of the pteridine group. Of several compounds synthetically made, it has been the most effective and yet most toxic agent in its action on the leukemic process.

Farber and co-workers first employed aminopterin in the treatment of acute leukemia of children in December 1947. In June 1948, they reported their observations on 16 leukemic children treated with this drug.[1] Ten of their patients showed clinical and hematologic evidence of significant improvement lasting as long as three months, at the time of the report. They noted several facts resulting from treatment: 1. Leukocyte counts tended to return to normal whether initially elevated or depressed. 2. The percentage of immature lymphocytes decreased and "blast" forms disappeared from the peripheral blood. 3. The hemoglobin content and the erythrocyte and platelet counts approached normal. 4. The bone marrow showed a decrease or disappearance of leukemic cells. Variations from a hypoplastic to a normally appearing marrow were noted. 5. Toxic effects such as stomatitis or ulcerations of the mouth or gastrointestinal tract were frequent. Farber and co-workers concluded that, by use of the drug, temporary remissions could be produced not only once but several times in the same patient who responded favorably.

Further reports[3–6] soon were made by other investigators using the same drug with somewhat similar results. Remissions were noted by several observers in approximately a third of the patients treated. They also noted the hematologic and toxic effects of the

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drug. Stickney and co-workers[3] reported the appearance of megaloblasts and of hyperlobulated nuclei in the neutrophils of the bone marrow specimens of patients adequately treated with aminopterin and observed for several months by studies of the blood and bone marrow.

A subsequent report by Farber[2] appeared in February 1949. He had treated 60 children, suffering from acute leukemia, for three weeks or longer with aminopterin or two newer folic acid antagonists known as a-methopterin (4-amino-methyl-pteroylglutamic acid) and amino-an-fol (4-amino-pteroylaspartic acid). Half the patients showed improvement clinically and hematologically. Two children were living 1½ and 2 years, respectively, after the beginning of treatment with folic acid or its analogues.

The mode of action of these drugs is conjectural. Farber has said that it may involve interference with the biochemical system in such a way as to affect the leukemic cells particularly. Dameshek[7] has said that the various enzyme systems are affected by the drug, particularly those of the "blast" cells, and that its action is to "dampen the wildfire" that is the leukemic process without extinguishing it. The toxicity of the drug may finally kill the patient if it is given in amounts sufficient to subdue the leukemia.

The interest of the authors was aroused by the foregoing publications and a study of the use of aminopterin* was begun in June 1948. Since that time continuous observations have been made on 21 children with acute leukemia diagnosed by physical examination as well as by examination of the peripheral blood smears and bone marrow and followed with repeated clinical observations and studies of the blood and marrow.

The ages of these patients varied from 16 months to 11½ years, all but 6 children being 5 years of age or less. Males predominated 2:1, which is a higher ratio than is generally reported in leukemia in this age group. The children were known to have had their disease for 10 days to 8 months before coming here. The type of leukemia was classified as acute lymphatic on the basis of the morphologic appearance of the blood and bone marrow. Eight children had elevated leukocyte counts, and an equal number had subnormal leukocyte counts at the time of admission to the clinic; the remainder had normal counts. Many of the children had been treated previously with blood transfusions, penicillin and various drugs intended to correct their anemia.

The following procedure was employed: After careful physical examination had been done, the hemoglobin content and the erythrocyte, leukocyte and platelet counts of the peripheral blood were determined. A differential count was done on the blood smear and the variety and number of immature leukocytes were noted. Examinations of the bone marrow were carried out on all children initially and at frequent intervals that varied from two weeks to a month as treatment was carried on. The period of treatment varied from 11 days to more than 12 months. The best result was obtained after the last-mentioned period of treatment of a child who is still living and appears well clinically. The average patient received treatment for two to four months.

The toxic effects of the drug were ulcerations of the buccal mucosa and edges of the tongue in more than half the patients. These were seldom seen when the total dose of aminopterin was less than 10 mg. Bleeding from the gastrointestinal tract was frequently encountered; it was found at postmortem examination in every one of the 12 patients examined at the clinic. One may argue that intestinal bleeding results from the leukemic process of infiltration of the bowel. The pathologic picture would tend to show that the nature and extent of the bleeding in the gastrointestinal tract in

* Material used in this study was supplied by Lederle Laboratories, Pearl River, N.Y.

these patients exceeded that formerly found in leukemic patients untreated with aminopterin.

Diarrhea was not unusual. It often accompanied the initial administration of the drug and was relieved by its discontinuance. Abdominal pain and distention were noteworthy in several patients. Alopecia occurred in six children and was marked in one child. Hypoplasia of the bone marrow and a severe degree of leukopenia resulted from prolonged administration or from large doses of the drug. The use of the drug was discontinued in only two patients who did not seem to respond after an adequate trial of three and five weeks, respectively.

Eighteen of the 21 patients treated showed one or more evidences of toxicity of the drug during their course of treatment. In all cases except the terminal ones, it was possible to stop the use of the drug and allow the patients to recover from the toxic effects of its administration. In many instances a secondary beneficial effect was noted in the blood and clinical condition of the patient after use of the drug was discontinued.

Most of the children were started on 0.5 to 1 mg. of aminopterin a day by intramuscular injection and treatment was continued until the leukocyte count became low or there appeared oral lesions of sufficient extent to cause pain and interfere with the taking of food. Hematologic studies were done on alternate days and the dose of the drug was varied according to the results of such studies. It was usually possible to continue use of the drug in reduced dosage such as 0.5 mg. on alternate days. In instances of severe toxic effect, withholding the drug for a week to 10 days usually afforded sufficient time for the toxic effects to abate and permit resumption of use of the drug.

Most of the children were ambulatory once the maintenance dose of the drug had been established, except in the terminal phases of the illness. They were therefore treated as outpatients, coming in on alternate days for studies of the blood and injections of aminopterin.

The dose tolerated varied greatly from child to child. Some were able to take daily injections of aminopterin 1 mg. for a month or more with no evidence of toxicity while others could tolerate only 5 to 10 mg. as a total dose before ulcers of the mouth or severe leukopenia developed. There could also be noted a diminution in size of the liver, spleen and lymph nodes when the response was favorable, and there is roentgenographic evidence of this in two of the patients. The maximal dose given any of the patients was 86 mg., which was received by a child whose blood seemed to show little if any benefit from the drug during the six months that she was treated. She received as much as 2 mg. of aminopterin a day over a short period.

The plan was to give treatment as indicated by the clinical state of the patient. Enough of the drug was given to initiate a favorable response clinically as well as hematologically and administration was continued until toxic effects severe enough to warrant withholding it were noted.

The total dose of drug varied widely from patient to patient and could be found only by clinical trial. As much as 3 mg. daily was given without benefit to a child who was mortally ill with acute leukemia and who had a greatly elevated leukocyte count. A daily dose of 1 mg. was given to several children for more than a month at one time. More aminopterin was given to the patients whose disease was responsive to treatment and who therefore lived long enough to be able to take more of the drug. It was noted, in some instances, that beneficial effects would persist for several weeks after use of aminopterin was discontinued.

Remissions were characterized by improvement in sense of well-being of the patient, by diminution in size of the liver, spleen and lymph nodes, by relief of pain in the bones caused by leukemic infiltration and by a beneficial effect on the blood so that the anemia improved, the bleeding tendency decreased, the number of immature cells diminished and the number of neutrophils increased. The bone marrow showed a decrease in the number of immature cells and a noticeable increase in erythroid regeneration with the appearance of megaloblasts in some instances. It was felt that three distinct remissions, of two to four months' duration, were observed in one patient, and one remission in each of nine other patients. These have lasted from one to three months, two patients enjoying a three month remission after taking 12 to 38 mg. of aminopterin.

TABLE I

AMINOPTERIN THERAPY FOR ACUTE LEUKEMIA: RESULTS OF TREATMENT OF 21 CHILDREN, JULY 1948–JUNE 1949

	Duration of Treatment				Total
	Less than 1 mo.	1 mo. to 3 mos.	3 mos. to 6 mos.	6 mos. or more	
Patients	8	4	5	4	21
Total dose, mg.	3.5–21	20.5–31	24–86	35–89	
Patients having complete remissions	0	1	2	2	5
Patients having partial remissions	0	2	2	1	5
Patients having toxic effects	6	4	4	4	18
Duration of disease, mos.	1–9	5–9	8–12	7–15	
Deaths*	8	4	4	2	18

* The 3 patients who were still alive at the time this paper was written have subsequently died of their disease.

Diamond[8] found that spontaneous remissions lasting 10 weeks occurred in 10% of 300 cases of leukemia studied by him before the advent of aminopterin therapy. Our results showed that 10 patients of the 21 treated obtained at least one remission either partial or complete. A complete remission was characterized by definite improvement clinically and hematologically for periods varying from one to three months. Partial remissions occurred in five patients whose improvement did not include all these factors. This is a significant improvement on Diamond's figures for the untreated group. It must be admitted that our series is far too small to permit drawing any valid conclusions at this time.

All our patients underwent blood transfusions when their anemia or tendency to hemorrhage warranted such treatment. Penicillin was administered to all who had continually low neutrophil counts or who had an infection.

It is of interest to know the duration of the disease in these patients in order to form

some idea of the effectiveness of treatment. The duration in this series varied from one month in the most acute leukemia to more than a year in two patients who are still under treatment. Obviously, more time will be needed to settle the question of the value of a new drug in the treatment of a condition which may not prove fatal for a considerable time even if untreated.

Of the 21 children in this study, 18 have died of their disease and 3 are continuing treatment with aminopterin at the clinic or elsewhere.*

Of the 4 patients who have been under treatment for 6 to 12 months, 2 survive and are still undergoing aminopterin therapy; of these, 1 is improved and 1 is unimproved. Table I summarizes the results of the foregoing study.

In conclusion, during the last 12 months aminopterin has been used for varying periods in the treatment of 21 children with acute leukemia. The drug has been found to have differing degrees of toxicity for different patients but toxicity appeared in practically all if sufficient drug was given. It is felt that a beneficial effect has been observed in 10 of the 21 patients treated. This figure is comparable to those reported by other investigators. As these results are better than have been obtained by previous forms of treatment of this disease, further studies in this direction are indicated.

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SPANISH ABSTRACT

Observaciones sobre Leucemia Aguda en Niños Tratados con Acido 4-Aminopteroilgluamico

Durante los últimos 12 meses se ha usado la aminopterina en diferentes períodos en el tratamiento de 21 niños con leucemia aguda. Se ha encontrado que la droga tiene diferentes grados de toxicidad para diferentes pacientes; pero apareció toxicidad en casi todos si se les daba suficiente droga. Se cree que se ha observado un efecto benéfico en 10 de los 12 pacientes tratados. Esta figura es comparable con los que otros investigadores han reportado. Como estos resultados son mejores que los que han obrenido con previas formas de tratamiento de esta enfermedad, se recomienda se hagan más estudios en esta dirección.

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* The 3 patients who were still alive at the time this paper was written have subsequently died of their disease.

ELECTROLYTE AND NITROGEN BALANCE STUDIES IN INFANTS FOLLOWING CESSATION OF VOMITING

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THE BIOCHEMICAL changes which accompany vomiting resulting from pyloric obstruction or other causes in animals and in man were first clearly elucidated by the studies of Gamble and his predecessors and of certain of their contemporaries.[1-9] It is now commonly recognized that ligation of the pylorus or other obstruction of the upper gastrointestinal tract is shortly followed by an outpouring of body fluid into the lumen. This fluid contains considerable amounts of chloride and of sodium in addition to the other constituents present in lesser concentrations in the extracellular phase. As a result, the serum levels of these two extracellular electrolytes decline. The drop is greater in the case of chloride, since losses of this ion in gastric secretions exceed those of sodium. The serum bicarbonate content usually rises, resulting in the alkalosis, with or without attendant pH changes, which characterizes prolonged loss of gastric secretions. Gamble as well as Peters and others have considered this to represent in the main a compensatory adjustment which restores the anion concentration to the level of the fixed base.[10,11] With prolonged losses of extracellular fluid through the stomach wall, renal failure and azotemia frequently supervene. The coincidental rise in the undetermined anion fraction may be of sufficient magnitude to cancel the alkalosis, or even to replace it with acidosis (Hartmann[12]). All these changes, as first demonstrated by Hartwell and his co-workers, are frequently reversible following prompt and adequate replacement of the deficits of water, sodium and chloride.[1,2] Application of these principles in the therapy of pyloric obstruction in infants has been associated with a decrease in the mortality rate at the Children's Hospital[13] as well as in other institutions.

Subsequent to these fundamental studies, it has become increasingly evident that gastric secretions contain considerable amounts of potassium in addition to sodium and to chloride (Bliss,[14] Austin and Gammon[15] and Ingraham and Visscher[16]). It is now unquestioned that losses by this route together with inanition may contribute to, or actually produce, deficits of body potassium. These are known to be associated at times not only with periodic paralysis, but also with certain pathologic changes in the electrocardiogram and even in the myocardium itself (Darrow,[17] Danowski *et al.*,[18] Tarail and Elkinton[19]). In view of these facts, the water, nitrogen, potassium and other electrolyte changes which occur in upper gastrointestinal tract obstruction have been re-evaluated in infants admitted for treatment of prolonged vomiting.

MATERIALS AND METHODS

One female and 6 male infants, 3 wks. to 14.5 mos. of age, have been studied in all but 1 instance by the balance method during intervals of 3 to 10 days. Six of these were proved to have pyloric

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obstruction at operation. The remaining patient, the oldest of the group, had an undiagnosed illness characterized by protracted vomiting and intermittent diarrhea. The clinical histories have been summarized in the appendix. Each patient ceased vomiting following admission coincident with the withdrawal of all intake by mouth. Parenteral fluid therapy during the initial days of study followed the principles generally observed in this hospital at that time. These were characterized in the main by attempts to provide sufficient water and some of the carbohydrate necessary to meet daily needs. Physiologic saline solution made up only a small portion of the intake. Potassium and other electrolytes were administered, with the exception of 1 case, only in the small amounts in which they are present in Hartmann's and similar solutions. Following operation in the pyloric obstruction cases, and at an empirically determined time in the 1 other patient, fluids and food were restarted *per os* and increased to a full complement as tolerated.

Throughout each study careful measurements were made of the body weight and of the intake. Catheterization and special nursing care assured, as far as can be determined, complete collections of urine and of stools. These excreta were pooled separately at intervals into periods up to 2 days long, marked by withdrawal of venous blood for analyses. The output of chloride, sodium, potassium and nitrogen in urine and in stools was measured in duplicate or in triplicate by methods described in previous publications from this laboratory.[18, 20] The whole blood nonprotein nitrogen and the water, chloride, sodium and potassium levels in the serum were also determined. Positive or negative external balances of nitrogen, sodium and of potassium were apportioned between cells and extracellular fluid in accordance with the usual procedure, employing the chloride space as an index of extracellular volume.[17, 18, 21, 22] The balances of nitrogen have been corrected for alterations in the nonprotein nitrogen distributed in the body fluids. The changes in cell potassium as tabulated represent balances in excess of those associated with the anabolism or catabolism of protein. For this purpose a K:N ratio of 2.38 mEq.:1.0 gm. has been used.

Results

A. Results of Serum and Blood Analyses Following Protracted Vomiting: A variety of serum electrolyte patterns was initially found in this group of infants (Table I). In the majority of subjects, however, the serum chloride concentration was characteristically decreased and the serum bicarbonate content distinctly above normal. The sodium in serum varied between 123 and 152 mEq./l., a range which distinctly exceeds the values in healthy individuals reported by Hald and her coworkers,[23] but most of the concentrations were between 130 and 140. More than half of the patients had at the start of the study abnormally low levels of serum potassium. Clear evidence of plasma dehydration was present in only 1 patient, R. L.; in the others, the serum water content was found to be either within normal limits or actually elevated. Azotemia, 44 mg.%, had developed in only 1 of the patients, T. B.

B. External Balance Data (Tables II and III, Chart I): In Table II the intake of water, electrolytes, carbohydrate and nitrogen has been summarized. As a result of the general plan of therapy described in brief earlier, the patients received 115 to 234 cc. of fluids/kg./calculated 24 hr. period. This contained on the average 15 to 42 mEq. of sodium and comparable amounts, 21 to 41 mEq., of chloride. A number of the patients had during the first few days of study no significant intake of potassium. This was particularly notable in the case of 4 of the subjects with pyloric obstruction (T.B., D.He., R.L. and P.Z.), whose daily intake of potassium in the periods prior to operation was usually only a fraction of a milliequivalent. The others received more substantial amounts of this cation in food or, in D. Hu., in the form of KCl added to the parenteral fluids. The patterns of nitrogen intake are similar to those just described for potassium. In addition, all patients received glucose or other carbohydrate, though the total daily intake was frequently low.

The balance data presented in Table III are calculated from the intake and output listed in Table II and include, as indicated in the footnotes to the tables, corrections for losses in stools and in serum withdrawn for analyses. It is immediately apparent that, with but few exceptions, a positive external balance of chloride and of sodium was recorded during each interval of study. During the earlier periods with a limited intake of potassium the external balances of this cation were usually negative (Table III). It should be pointed out, however, that the total amount of potassium lost was not large and that this loss occurred often at the rate of only a fraction of a milliequivalent/calculated 24 hrs. of observation. Furthermore, even though the urinary excretion of potassium increased with the administration of larger amounts of this electrolyte, a distinct lag is evident. Thus, in patients T.B., D.Hu., M.M. and A.R., subjects who were given considerable amounts of potassium during the

TABLE I

BODY WEIGHT AND ANALYSES OF BLOOD AND SERUM AT START OF AND DURING BALANCE STUDIES*

Patient (Sex—Age)	Time from start (hrs.)	Body wt. kg.	Blood NPN mg./100cc.	Serum HCO_3 mEq./l.	Serum Cl mEq./l.	Serum Na mEq./l.	Serum K mEq./l.	Serum H_2O gm./l.
T.B.	0	2.79	44	37.3	78.0	139	4.3	930
(M—3.5 wks.)	0– 20	—	41	32.0	79.1	134	3.2	944
	20– 42	—	32	28.2	88.4	130	3.3	920
	42– 68	2.90	26	27.5	92.3	131	3.4	933
	68– 90‡	—	—	26.8	95.5	131	2.8	946
	90–116	3.01	26	24.5	94.7	134	4.0	942
	116–140	—	—	25.0	99.2	141	4.9	945
	140–188	3.04	—	22.5	98.1	136	4.6	937
	188–212	—	—	21.0	96.8	131	5.1	931
D.He.†	0	2.77	39	25.3	96.6	129	3.3	947
(M—5 wks.)	0– 15	—	35	24.6	97.9	136	3.6	942
	15– 41	3.07	38	21.7	102.3	133	3.6	937
	41– 66‡	—	—	20.7	104.1	133	4.0	951
D.Hu.	0	2.33	36	31.4	90.9	152	2.7	949
(M—6 wks.)	0– 20	—	—	24.7	100.7	131	2.1	950
	20– 45	—	26	21.2	100.7	132	3.9	946
	45– 69	—	—	20.7	104.5	131	5.3	941
	69– 93‡	2.61	20	21.8	101.4	130	5.5	—
	93–117	2.71	28	19.4	105.4	140	3.9	954
	117–141	2.49	39	22.8	104.7	133	4.5	933
R.L.	0	—	—	31.2	73.3	123	3.6	913
(M—6 wks.)	0– 48	—	—	31.2	85.4	129	3.5	936
	48– 72	—	—	32.9	92.0	134	2.1	—
	72– 96‡	—	—	31.3	93.3	130	2.8	—
	96–168	—	29	24.0	103.0	130	4.5	935
P.Z.	0	3.08	35	—	102.8	134	4.2	948
(F—3 wks.)	0– 13	—	25	24.6	103.3	136	4.9	948
	13– 36	—	21	21.7	104.2	129	4.3	942
	36– 61	3.07	—	21.1	107.5	130	3.7	949
	61– 84	3.15	23	20.1	106.8	136	5.1	944
	84–108	3.21	—	17.7	107.3	141	5.0	950
	108–131	3.18	—	19.8	107.6	139	4.0	949
	131–155§	—	—	20.5	108.5	133	4.3	—
M.M.	0	3.52	34	35.7	81.4	137	2.6	940
(M—7 wks.)	0– 23	3.59	—	29.3	108.0	138	2.7	947
	23– 47	—	—	28.8	98.1	145	2.0	944
	47– 72‡	4.00	20	27.4	98.5	136	2.5	—
	72–125	4.04	22	30.2	98.3	137	2.5	942
A.R.	0	9.74	27	40.1	81.0	136	1.6	—
(M—14.5 mos.)	0– 6	—	—	—	—	139	1.7	946
	6– 22	9.60	—	41.6	81.1	134	2.2	946
	22– 48	9.89	24	33.7	95.4	131	2.1	946
	48– 72	9.95	—	33.5	88.0	132	3.0	948
	72–120	9.83	—	24.7	99.4	138	5.5	938
	120–144	9.49	—	21.2	97.1	132	5.1	944
	144–168	9.55	—	20.3	99.7	131	5.2	937

* Refer to values observed at start (0 hr.) and at end of each individual period.

† No parenteral fluids prior to balance study. All the other patients received parenteral fluids in unmeasured amounts between the time of admission and the start of the balance study.

‡ Indicates period during which operation for relief of pyloric stenosis was performed.

§ Not operated until study had been terminated.

TABLE II

PARENTERAL AND ORAL INTAKE AND URINE OUTPUT DURING BALANCE STUDIES

Patient	Time from start (hrs.)	Intake						Urine Output				
		H_2O ml.	Cl mEq.	Na mEq.	K mEq.	N gm.	CHO gm.	Vol ml.	Cl mEq.	Na mEq.	K mEq.	N gm.
T.B.	0– 20	550	21	20	0.4	0	21	216	1	10	3.1	0.5
	20– 42	715	20	20	0.5	0	30	230	1	4	1.2	0.4
	42– 68	525	20	20	0.5	0	20	175	1	2	0.3	0.2
	68– 90‡	464	13	13	1.4	0.4	18	202	2	3	0.6	0.3
	90–116	893	25	22	10.5	1.4	49	115	1	1	0.1	0.1
	116–140	967	36	32	18.7	2.5	68	258	2	3	0.6	0.2
	140–188	1263	43	39	28.3	4.1	81	333	17	27	7.3	0.6
	188–212	425	7	6	8.4	1.2	10	205	14	10	13.0	1.0
D.He.	0– 15	440	20	19	0.5	0	16	215	1	5	1.8	0.4
	15– 41	610	28	28	0.8	0.3	20	220	5	7	1.7	0.4
	41– 66‡	462	12	12	1.5	0.2	20	166	2	3	1.8	0.6
D.Hu.*	0– 20	726	65	64	1.4	0.2	14	215	8	12	1.5	0.3
	20– 45	370	18	9	9.0	0	16	228	15	15	1.0	0.1
	45– 69	845	42	20	23.3	0.2	35	447	17	15	5.8	0.2
	69– 93‡	700	45	35	9.4	0	24	183	8	6	3.9	0.1
	93–117	477	36	35	2.2	0.4	13	253	10	11	6.4	0.1
	117–141	314	10	8	12.4	1.7	29	260	16	24	5.5	0.6
R.L.†	0– 48	1180	44	47	0.6	0	43					
	48– 72	362	15	17	0.5	0.3	11					
	72– 96‡	679	21	23	10.2	1.7	24					
	96–168	1790	37	35	35.2	5.2	46					
P.Z.	0– 13	275	11	10	0.3	0	11	59	2	4	0.9	0.2
	13– 36	480	16	16	0.4	0	19	186	8	9	2.1	0.3
	36– 61	605	25	24	0.7	0	23	194	6	5	1.4	0.2
	61– 84	525	20	20	0.5	0	20	213	5	5	0.4	0.1
	84–108	550	25	24	0.7	0	20	268	4	5	0.2	0.1
	108–131	550	25	24	0.7	0	20	235	15	16	0.8	0.2
	131–155	550	25	24	0.7	0	20	425	19	20	1.1	0.3
M.M.	0– 23	650	39	39	0	0	20	68	2	3	0.4	0.2
	23– 47	680	24	26	0.2	0.4	24	214	6	8	0.6	0.3
	47– 72‡	719	32	34	1.2	0.9	24	248	7	12	0.3	0.2
	72–125	608	21	20	7.0	1.0	32	110	4	5	0.1	0.1
A.R.	0– 6	1025	63	75	2.4	0.7	23	265	27	32	0.9	0.4
	6– 22	650	44	52	1.6	0	24	660	75	89	1.9	0.7
	22– 48‡	780	61	70	9.1	1.0	25	260	8	35	1.9	1.3
	48– 72	1020	23	18	27.3	3.8	45	130	2	10	0.9	1.0
	72–120	2300	52	42	62.4	8.6	99	660	4	47	6.7	2.8
	120–144	690	15	12	17.8	2.5	30	170	2	8	9.3	1.3
	144–168	1265	31	25	37.7	5.2	45	220	9	5	10.9	1.6

* KCl added to infusions between 20th and 93rd hrs. in amounts sufficient to give solutions of potassium containing 8.5 to 23.7 mEq./l.

† Patient not on complete balance study and hence only sporadic urine specimens were available.

‡ Oral intake begun during this period.

later periods of study, urinary losses of this cation increased only after a delay of 1 or more days and in no instance equalled the intake in magnitude (Table II). This resulted, of course, in the positive external balances of potassium presented in the succeeding table. Save for 1 period (22 to 48 hrs.) in subject A.R., the largest infant in the group, the external balance of nitrogen became positive whenever the intake during any particular period was 0.4 gm. or greater (Table II and III). In view of the fact that no marked fluctuations were observed in the nonprotein nitrogen levels in body fluid, the external balance of nitrogen agreed closely both in direction and in order of magnitude with changes in cell nitrogen (Table III).

C. Apportionment of External Balances Between Extracellular Fluid and Cells: As might be expected from the positive balances of chloride associated with only moderate changes in the serum concentrations of this ion, the chloride space expanded almost uninterruptedly in each of the studies. This is clear from the positive balances of extracellular water in Table III, based on alterations in the chloride space. Assuming that the extracellular volume actually expanded as recorded, it would then appear that in most periods the extracellular content of sodium and of potassium progressively increased. At the same time it is also evident that during these intervals sodium was usually transferred out of cells, while cell potassium increased whenever significant amounts of this ion were retained

TABLE III

RESULTS OF CALCULATIONS OF EXTERNAL, EXTRACELLULAR AND INTRACELLULAR BALANCES

Patient	Time from start (hrs.)	Balance									
		External*				Extracellular			Intracellular		
		Cl mEq.	Na mEq.	K mEq.	N gm.	H_2O l.	Na mEq.	K mEq.	N gm.	Na mEq.	K† mEq.
T.B.	0– 20	+20	+ 9	− 2.7	−0.5	+0.22	+26	+0.2	−0.4	−17	− 1.9
	20– 42	+19	+15	− 0.7	−0.4	+0.11	+15	+0.6	−0.2	0	− 0.8
	42– 68	+19	+17	+ 0.2	−0.2	+0.16	+20	+0.5	−0.1	− 4	− 0.1
	68– 90	+11	+10	+ 0.8	+0.1	+0.09	+10	−0.2	+0.1	0	+ 0.8
	90–116	+23	+21	+10.4	+1.3	+0.22	+33	+2.0	+1.3	−12	+ 5.3
	116–140	+33	+28	+18.1	+2.3	+0.25	+44	+2.5	+2.3	−16	+10.1
	140–188	+21	− 6	+19.4	+2.3	+0.20	+22	+0.4	+2.3	−28	+12.6
	188–212	− 8	− 6	− 4.6	+0.2	−0.06	−15	+0.6	+0.2	+10	− 5.7
D.He.	0– 15	+18	+13	− 1.3	−0.4	+0.16	+25	+0.7	−0.3	−12	− 1.3
	15– 41	+22	+20	− 0.9	−0.1	+0.16	+20	+0.6	0	0	− 1.5
	44– 66	+10	+ 8	− 0.3	−0.4	+0.08	+10	+0.6	−0.5	− 2	+ 0.3
D.Hu.	0– 20	+56	+51	− 0.1	−0.1	+0.47	+54	+0.7	0	− 3	− 0.8
	20– 45	+ 2	− 8	+ 8.0	−0.1	+0.01	+ 2	+1.5	0	−10	+ 6.5
	45– 69	+24	+4	+17.5	0	+0.17	+23	+2.1	0	−19	+15.4
	69– 93	+36	+28	+ 5.5	−0.1	+0.36	+45	+2.2	0	−17	+ 3.3
	93–117	+24	+23	− 4.2	+0.3	+0.16	+34	−1.6	+0.2	−12	− 3.1
	117–141	− 7	−17	+ 6.3	+1.1	−0.08	−17	+0.7	+0.9	0	+ 3.5
P.Z.	0– 13	+ 8	+ 5	− 0.6	−0.2	+0.06	+ 9	+0.7	0	− 3	− 1.3
	13– 36	+ 8	+ 6	− 1.7	−0.3	+0.06	+ 5	0	−0.2	+ 1	− 1.2
	36– 61	+18	+17	− 0.7	−0.2	+0.13	+17	0	−0.2	0	− 0.2
	61– 84	+15	+14	+ 0.1	−0.1	+0.13	+22	+1.7	−0.1	− 8	− 1.4
	84–108	+19	+17	+ 0.5	−0.1	+0.16	+26	+0.9	−0.1	− 9	− 0.2
	108–131	+ 9	+ 6	− 0.1	−0.2	+0.07	+ 7	−0.7	−0.2	− 1	+ 1.1
	131–155	+ 5	+ 3	− 0.4	−0.3	+0.03	− 2	+0.5	−0.3	+ 5	− 0.2
M.M.	0 –23	+35	+34	− 0.4	−0.3	+0.17	+23	+0.5	−0.2	+10	− 0.4
	23– 47	+18	+16	− 0.4	+0.0	+0.23	+39	0	+0.1	−22	− 0.6
	47– 72	+23	+20	+ 0.6	+0.5	+0.20	+19	+0.9	+0.6	+ 1	− 1.7
	72–125	+17	+14	+ 6.9	+0.8	+0.15	+23	+0.4	+0.7	− 9	+ 4.8
A.R.	0– 6	+35	+42	+ 1.5	+0.4	+0.39	+57	+0.7	+0.5	−15	− 0.4
	6– 22	−31	−39	− 0.3	−0.7	−0.35	−56	+0.2	−0.6	+18	+ 0.9
	22– 48	+53	+34	+ 7.2	−0.3	+0.27	+32	+0.4	−0.2	+ 2	+ 7.3
	48– 72	+ 1	+ 5	+23.5	+2.8	+0.16	+22	+2.3	+2.8	−16	+14.5
	72–120	+46	−7	+55.7	+5.8	+0.18	+41	+5.6	+5.8	−48	+36.3
	120–144	+ 1	+ 1	+ 4.9	+1.2	+0.05	− 9	−0.6	+1.2	+ 9	+ 2.6
	144–168	+21	+19	+26.7	+3.6	+0.12	+16	+0.9	+3.6	+ 3	+17.2

* External balances have been corrected for constituents in serum samples withdrawn for analyses and for losses in stools as follows: T.B., stool mixed with urine between 140 and 188 hrs. with volume of 220 cc. contained 15.8 mEq. Na, 1.6 mEq. K, 3.5 mEq. Cl, 1.1 gm. N; D.Hu., formed stools between 93 and 141 hrs. contained 0.7 mEq. Na, 0.6 mEq. K, less than 0.1 gm. N; A.R., stool between 48.1 and 72.1 hrs. as result of enema with distilled water contained 1.7 mEq. Na, 2.9 mEq. K, 19.0 mEq. Cl. A 2nd formed stool in period 120 to 144 hrs. contained 2.6 mEq. Na, 3.5 mEq. K, 10.8 mEq. Cl; M.M., formed stool between 47 and 72 hrs. contained 1.4 mEq. Na, 0.3 mEq. K, 1.2 mEq. Cl, 0.1 gm. N.

† Represents changes in cell potassium in excess of those associated with anabolism or catabolism of protein.

in the body. It should again be emphasized, however ,that these estimations are based upon acceptance of changes in the chloride space as a valid index of alterations in extracellular water. Whether this is justified will be discussed subsequently.

D. Changes in Serum Constituents in Relation to the Balance Data: It is to be noted that the positive external balances of sodium recorded in Table III in no instance resulted in hypernatremia. The retention of administered chloride served to restore to normal and, in 1 instance (P.Z.), to slightly elevated levels, the serum concentrations of this electrolyte. Changes in the serum bicarbonate are more difficult to categorize. If the usual range of values recorded by Hald et al. in healthy adults (approximately 27 mEq./l.[23]) is used as a point of reference, alkalosis disappeared in 1 to 3 days in all but infants R.L. and M.M. It subsequently declined in the former patient; in the latter, the study had to be terminated prematurely. However, sufficient information has now accumulated to indicate that in young infants of this age group, particularly in those on cow's milk formulae, the serum

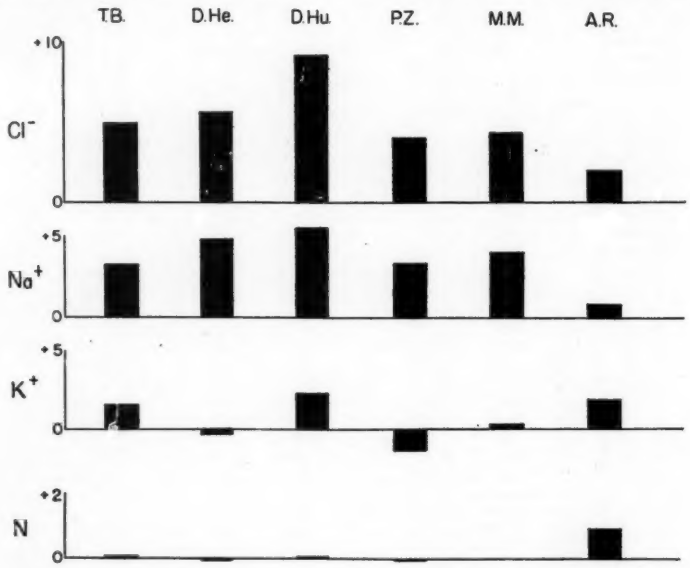

CHART 1. External balance of electrolytes and of nitrogen related to time and body wt. Cl^-, Na^+, K^+ balances are presented in mEq./24 hrs./kg. body wt; N in gm./24 hrs./kg. body wt. These values represent averages in each study.

bicarbonate level is much lower than it is in adults (Marples and Lippard,[24, 25] Hoffman, Parmalee and Grossman[26, 27]). If this is taken to represent a physiologic fact characteristic of healthy infants, then it obviously took much longer to correct the abnormal increases in the serum bicarbonate.

Insofar as serum potassium levels are concerned, if 3.5 mEq./l. is taken to be the lower limit of normal potassium concentrations in adult sera as a reference, it is apparent that, with but 1 exception, P.Z., all patients in this series either had hypokalemia at the start or developed it in the course of therapy. Actually this is all the more pronounced when it is recalled that in infants serum potassium levels are usually higher than in adults.[27] No accurate data are available on the events preceding the start of any particular study and hence hypopotassemia when present initially cannot be evaluated. However, the quantitative findings during the balance periods themselves clearly point to the etiology of at least some instances of hypokalemia. During these intervals diminished levels of potassium cannot be ascribed to continued losses of potassium in gastric secretions, since the patients did not vomit following admission. Neither did this lowering of serum potassium during the balance studies stem from persistent urinary excretion of this cation in significant amounts (Table II). There are, however, other possible explanations for this hypokalemia. It could have resulted from (a) dilution

of extracellular fluid with low potassium solutions, (b) transfers of potassium into cells, as demonstrated by Fenn[28] in the course of glycogen formation or by Elkinton and Winkler[21] during the reconstitution of tissue, and (c) a combination of the preceding 2 possibilities. In view of the undue rises in the chloride space quantitative definition of the relative importance of these processes is certainly unjustified. However, inasmuch as the subjects were in positive water balance and since it is known that convalescence with glycogen formation and tissue restoration are accompanied by the entry of potassium into cells, it seems reasonable to suggest that both processes contributed to the hypokalemia to an unidentified degree. Far more important, however, is the finding that all patients who received significant amounts of potassium developed a positive balance of this cation and serum levels returned to normal.

Discussion

Probably the weakest link in the data just presented is the assumption that in these studies the alterations in the chloride space mirror changes in the extracellular fluid volume. This becomes particularly clear when the final extracellular volumes in the various studies are presented as percentages of the body weight. Thus, beginning with an assumed chloride space of 15% of the initial body weight, it was found that during the course of the studies this value had expanded up to as high as 57% of the final body weight. This falls outside the usual range of about 20% assigned to nonedematous adult subjects and the slightly higher value, 25%, thought to be characteristic of infants.[29, 30] The lower final figures in this series, 24, 23, 34 and 32% of the body weight in patients D.He., A.R., P.Z. and M.M., respectively, are acceptable if it is assumed that overexpansion had been produced in some instances. The higher values appear unreasonable. The initial impulse to assign the unduly high chloride space volumes to undetected losses of this index ion in excreta is probably unjustified because of (a) the care exercised in collecting complete specimens and (b) the finding that similar overexpansion of the extracellular volume has been recorded in the studies of Hoffman[26] and of Darrow.[31] Losses of chloride and other electrolytes through the skin certainly can occur with or without sweating (Swanson and Iob[32] and others[33, 34]) and this offers one possible explanation. Our studies were conducted during the fall and winter months. It is more likely, therefore, that changes which appear to be unduly extensive are attributable to cumulative errors in the balance studies or to transfers of chloride into cells. The relative importance of these factors has been evaluated by Elkinton, Winkler and Danowski.[35]

Obviously the important question from the point of view of the calculations presented in this paper revolves not so much about the accuracy with which changes in the extracellular space can be measured but concern rather the validity of certain deductions based upon changes in the chloride space. However, even with false high estimates for this latter figure, irrespective of their etiology, the conclusions which have been reached are fundamentally sound. This is a reasonable stand primarily because the vicissitudes in the chloride space, with but few exceptions, altered merely the magnitude and not the direction of the exchanges of electrolytes and of nitrogen between extracellular fluid and cells. This is particularly true in the case of the positive intracellular potassium balances which become all the more pronounced, if it is granted that the actual extracellular volume is smaller than that estimated from changes in the chloride space. On the other hand, the calculated movements of sodium out of cells will on the same score prove unduly high. However, this particular transfer of electrolyte from cells to extracellular fluid as studied in this laboratory has frequently not been equivalent in magnitude to potassium movements into cells and has even gone in the same direction.[18, 22] The findings of Conway and Hingerty[36] do suggest a lag in the extrusion of intra-

cellular sodium during replacement of cell potassium as a possible explanation, but it must be kept in mind that the net exchanges of intracellular sodium usually represent a small difference between two large numbers and hence are particularly subject to errors. Sodium balances comprise, however, a subsidiary point in the principles under discussion.

The chief point to be emphasized is based upon the metabolism of potassium, particularly since the importance of losses of sodium in the physiologic changes which follow upon salt depletion has been established in a series of studies by Elkinton,[37] Danowski[38] and Winkler.[39] It is admitted that no data are at hand on the losses of potassium which occurred during the periods of vomiting in our patients. Collateral evidence now available indicates that these must have been considerable, not only in gastric juice, but perhaps in urine as well.[19] Such antecedent losses seem highly probable in view of the retention of potassium in this particular series of patients whenever potassium was administered. As has already been mentioned, a positive balance in other diseases has been considered to be indicative of such a deficiency.[17,18] In view of the physiologic and pathologic changes which accompany decreases in the body stores of potassium, the inclusion of sufficient amounts of this electrolyte in the therapeutic regimen is clearly indicated.

Summary

Abnormally low levels of serum potassium were observed prior to or during therapy of infants with a history of prolonged or recurrent vomiting.

Balance studies indicate that either dilution of body fluids with low potassium solutions, or transfers of potassium into cells, or both processes were responsible for the hypokalemia.

The probable existence of deficits of body potassium incurred prior to the balance studies and their therapeutic implications have been discussed.

Acknowledgment

The authors are in debt to the following colleagues on the staff of Children's Hospital for their cooperation in these balance studies: Drs. J. Barry, L. Bachman, T. O. Elterich, E. S. A. King, A. D. Kuhns, J. McAleese, E. L. Piper, C. J. Stoecklein and J. A. Wunderlich. They also wish to acknowledge in particular the assistance of the staff under the direction of Miss V. Mylrea, R. N., which provided nursing care for the majority of these infants.

Clinical Summaries

T.B. A 3½ wk. old male had vomited postprandially for 2 wks. Severely dehydrated with palpable pyloric tumor and visible peristalsis on admission. In 24 hrs. before the study he received 90 cc. of 1:1 5% glucose in H_2O and normal saline *s.c.* and oral glucose. Vomiting continued. Ramstedt operation 3 days after start of study.

D.He. A 5 wk. old male had vomited after feeding since 2nd day of life. On admission dehydration, emaciation, visible peristalsis and palpable tumor were noted. Oral feeding caused vomiting and no parenteral fluids were given until start of study 22 hrs. after admission. Ramstedt operation was done after 45 hrs. of study.

D.Hu. A 6 wk. old male admitted after 1 wk. of postprandial emesis with visible peristalsis and palpable pylorus. Born prematurely (6 wks.). During the 60 hrs. before study 50 cc. saline *s.c.* and 50 cc. 5% glucose in water q. 4 h. × 12 were given. Ramstedt operation on 4th day of study.

R.L. A 6 wk. old male had vomited occasionally since birth; after each meal for 1 wk. On admission he was malnourished and somewhat dehydrated. Peristalsis and tumor were noted. On oral feedings vomiting persisted for 24 hrs. when study was started. Ramstedt operation was performed on the 4th study day.

P.Z. A 3½ wk. old female had vomited after feedings since birth. Mild dehydration, peristalsis and a small tumor were found on admission. All oral feedings were vomited in 5 days prior to study. 80 cc. Hartmann's and 360 cc. 5% glucose were given *s.c.* during 24 hrs. before study. Ramstedt operation 48 hrs. after end of study.

M.M. A 6½ wk. old male was admitted after 3 wks. of postprandial emesis. Dehydration, visible peristalsis and pyloric tumor were present. In the 24 hrs. prior to study he received 225 cc. saline and 400 cc. 5% glucose in H_2O i.v. Ramstedt operation was performed after 2 days of study.

A.R. A 14 mo. old male had had severe diarrhea for 5 days and vomiting for 4 days during pinworm therapy with enemata and an unknown medication. During the 1st 9 hospital days penicillin and parenteral therapy brought temperature to normal. During 12 hrs. prior to the study he received 200 cc. Hartmann's and 500 cc. 5% glucose in H_2O. Culminating in alkalotic tetany with convulsions, carpopedal spasm and cyanosis unrelieved by 0.3 gm. of calcium gluconate i.v. Study period—after 20 hrs. of parenteral therapy, oral feedings were started. Convalescence was uneventful and discharge diagnosis was acute gastroenteritis of unknown origin.

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SPANISH ABSTRACT

Estudios de Balance de Electrolito y Nitrogeno en Infantes Después de Cesar el Vómito

Los estudios de balance se han hecho en 1 hembra y 5 infantes varones con estenosis pilórica, lo mismo que otro con diarrea y vómitos de origen no diagnosticado. Al principio de los estudios individuales, pero después de la terapia con pequeñas cantidades variables de salina y glucosa la mayoría tenía hipocloremia y alcalosis; 1 azotemia, y 4 concentraciones bajas anormales de potasio de suero, y potasio de suero entre 123 y 152 mEq./1.

No habiendo vómitos durante los periodos de balance ya que la toma oral fué detenida hasta que la obstrucción había sido aliviada en los infantes con estenosis pilórica, y los síntomas gastrointestinales habían desaparecido en el otro niño. La terapia durante este tiempo consistió en glucosa parenteral, pequeñas cantidades de salina y en todos menos 1 caso, casi nada de potasio. La toma de potasio se volvió significativa al resumir la alimentación oral.

Todos los sujetos detuvieron el sodio y el cloruro. El espacio de cloruro, que se asume ser al principio 15% del peso de cuerpo original, se extendió progresivamente hasta que, en algunos casos, excedió por un margen considerable los volumenes generalmente designados al flúido extracelular.

La hipocalemia apareció o aumentó más en 6 pacientes, a pesar de que las pérdidas de potasio urinarias fueron tan bajas como una fracción de un miliequivalente por día. Cuando se administró el potasio, su excreción urinaria aumentó, pero no fué igual a la toma. Estos descubrimientos sugieren la existencia de deficits de potasio y la conservación renal de este catión. Estos datos no identifican las pérdidas renales y extrarenales de potasio antes de estos estudios. Ellos señalan una combinación de dilución de flúido extracelular y paso del potasio en las células como el mecanismo de hipocalemia durante la terapia.

125 De Sota Street

URETEROCELE IN INFANCY AND CHILDHOOD

By ROBERT E. GROSS, M.D., AND H. WILLIAM CLATWORTHY, JR., M.D.
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PEDIATRICIANS must be constantly aware of the fact that congenital abnormalities of the urinary tract are common and that they are often followed by pyuria and a wide variety of complaints. Of the various types of urinary tract obstruction, blocks at the uretero-vesical junction with formation of a ureterocele are relatively few in number, but they can lead to a high degree of renal damage. It is important to emphasize that they can be recognized easily and that they can be cured by relatively simple means.

During the past 20 years 21 cases of ureterocele have been treated at The Children's Hospital in Boston. During this same period there have been approximately 260,000 new admissions, an incidence of about one in 12 thousand patients. This rate of occurrence compares reasonably well with the statistical study of anomalies of the genitourinary system by Smith and Orkin[1] which was based on 18,400 admissions to the Royal Victoria Hospital, Montreal, in which there was only one case of ureterocele. Our series of cases is of particular interest because it focuses attention upon the lesion as it exists in young age groups. Our general experience coincides closely with the studies which have been made and admirably presented by Campbell,[2, 3] Goyanna and Greene,[4] Kickham,[5] Thompson and Greene[6] and others.[7]

Obstruction of a ureteral orifice inevitably leads to ureterectasia and hydronephrosis but it does not always produce a ureterocele. When stenosis of a ureteric orifice is accompanied by a weakness in the ureteric wall, there is a ballooning out of that portion of the ureter which passes through the bladder wall—which has the over-all effect of producing a "cystic" structure, one to several centimeters in diameter, which protrudes into the bladder lumen (Fig. 1). Ureteroceles are lined with the transitional, mucosal epithelium of the ureter and are covered externally by the mucosa of the bladder. They possess a thinned-out, interstitial mesenchymal layer of fibrous tissue and smooth muscle.

With few exceptions, ureteroceles have a congenital origin though they may be asymptomatic and unrecognized in early life. The lesions may be unnoticed for years until symptoms appear which are referable to superimposed infection, bladder irritation or advancing urinary tract obstruction. Various authors have indicated that ureteroceles might not be discovered until adult life, but the average age of the patients in this study at the onset of the presenting illness was 22 months; nine were less than 1 year. The youngest was 2 days of age, and the oldest was 6 years (Fig. 2). In these patients, the average duration of symptoms was nine months, with a range from six days to two years. The sex incidence is noteworthy, since the abnormality is much more common in females; 15 of the subjects were females and 6 were males. This ratio is in accord with the findings of Campbell,[2] Martius[8] and Thompson and Greene,[6] the latter series consisting largely of adult and adolescent subjects.

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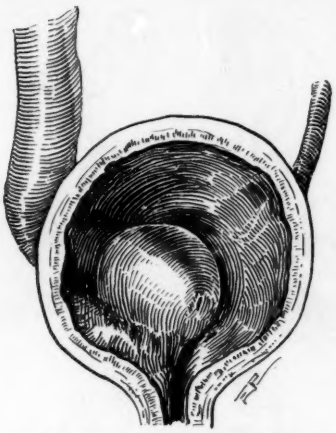

FIG. 1. Typical ureterocele. Ureteric orifice on right is tiny. That portion of ureter which courses through bladder wall has become dilated and forms mass which balloons into lumen of bladder.

The left side is most frequently involved. In this series, 13 ureteroceles were on the left, and 7 on the right; in one case there were bilateral abnormalities. Campbell,[2] in reporting 32 cases, found them equally distributed as to side, with 15% bilateral. Coinciding with our findings, Adams[9] and Thompson and Greene[6] list the more common location on the left.

In 12 of our 21 cases there were double ureters on one or both sides. When a ureterocele occurred on that side of the bladder which received double ureters, the ureterocele always arose from the lower ureteric orifice. In no instance with ipsilateral duplication of the ureters did the ureterocele arise from the upper ureteric opening (which, of course, drains the lower pole of the kidney on the affected side). Failure to recognize

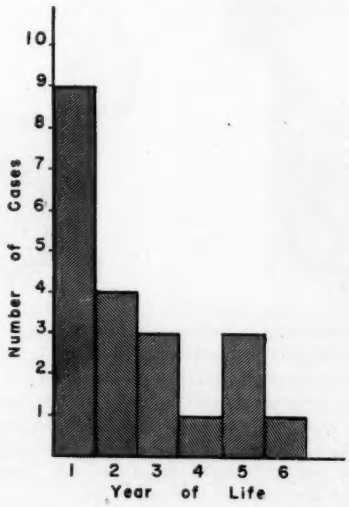

FIG. 2. Age of patients at beginning of symptoms from ureterocele.

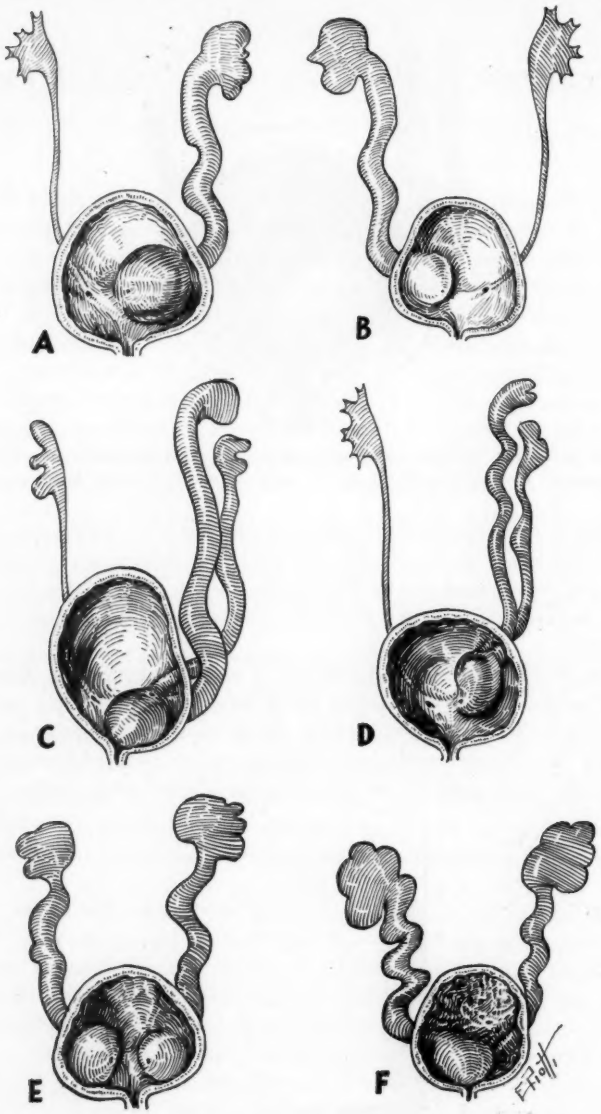

FIG. 3. Ureteroceles and associated pathology which were encountered in this series. A. Left ureterocele with left hydro-ureter and hydronephrosis. B. Right ureterocele with right hydro-ureter and hydronephrosis. C. Ureterocele from left lower ureteric orifice, partially compressing upper orifice on left side of trigone. Ureterocele partially blocks bladder outlet and produces mild hydronephrosis on right. D. Same as C, but ureterocele does not block bladder outlet and produces no pathology on patient's right. E. Bilateral ureteroceles with bilateral marked hydronephrosis. F. Ureterocele on patient's right with hydronephrosis on that side. Ureterocele blocks bladder outlet, gives obstructed trabeculated bladder and left hydronephrosis.

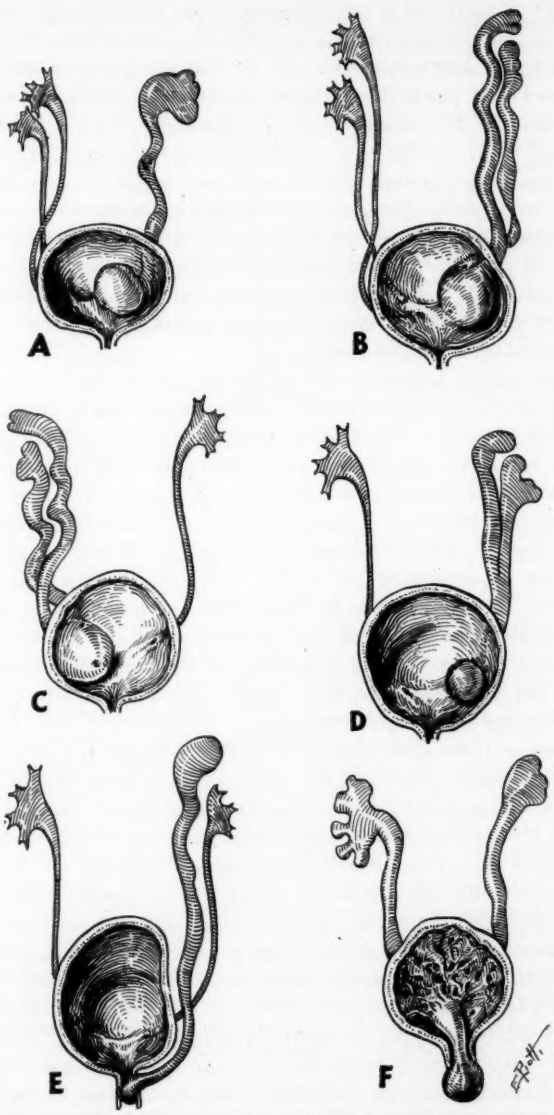

FIG. 4. Continuation of sketches of ureterocele and associated pathology which were encountered in this series. A. Left ureterocele and hydronephrosis. Right double, unobstructed ureters. B. Double ureters both sides, unobstructed on right. On left, ureterocele arises from lower ureteric orifice and by compression it blocks upper ureteric orifice, giving obstruction of both ureters on patient's left. C. Double ureter, right, with ureterocele at lower orifice, partially compressing superior ureteric orifice, giving dilatation of both ureters on right. D. Bifid ureter on left, with ureterocele at lower end of same. E. Double ureter on left, 1 ureter entering urethra and giving rise to ureterocele there. F. Right ureterocele prolapsed through female urethra, giving bladder obstruction and trabeculation, with bilateral hydronephrosis.

this fact can lead to confusion at the cystoscopy bench or operating table.

Seventy per cent of the patients were found to have other anomalies of the genitourinary tract. By far the most common of these were ipsilateral or contralateral duplication of the ureter and kidney pelvis. The frequent association of double ureters with ureteroceles is not unusual, but has been repeatedly emphasized by Patch,[10] Adams,[9] Campbell[2] and Goyanna and Greene.[4] This type of additional developmental anomaly should be suspected and searched for in every case wherein a ureterocele is found. Other anomalies discovered were ipsilateral uretero-pelvic obstruction due to fibrous bands; one case of ectopic pelvic kidney; one case of ureteral duplication wherein the left upper pole ureter entered the urethra where it formed a ureterocele bulging into the urethra and presenting at the urethral orifice.[11] It is important to emphasize that whenever a ureterocele is found, the entire urinary tract should be studied to gain a complete and accurate picture of the anatomic structure of the whole excretory system.

The pathologic changes associated with ureteroceles can be separated into two phases. The first are those which are directly attributable to obstruction of the urinary tract and the second are those related to superimposed infection which occurs with great frequency. Blockage of the ureter can lead to recurring abdominal or flank pain. In its early stages there may be little or no dilatation of the renal pelvis or upper part of the ureter but blockage of long standing is accompanied by severe degrees of dilatation of the upper urinary tract and even by advanced destruction of renal parenchyma. When an ipsilateral duplication of the upper urinary tract exists, the ureterocele mass may bulge upward and partially block the second ureter by compression—so that both ureters on that side will be found dilated. If a ureterocele is of sufficient size it can flop over and plug the bladder outlet and thereby produce obstruction of the bladder and lead to bilateral hydronephrosis and ureterectasia. In rare instances a ureterocele may actually prolapse through the urethra and present itself externally.

Secondary changes from superimposed infection are found in a high percentage of patients with a ureterocele because of the stagnation or reduced flow of urine through some part of the excretory tract. Fever, malaise, loss of weight, anorexia or vomiting, leucocytosis and urinary frequency are commonly found. In all but one of the subjects pyuria and bacilluria were present at the time of hospital admission.

For the sake of classification, the lesions can be divided arbitrarily into three groups: (1) those with ipsilateral obstruction of the involved ureter (9 cases); (2) those with ipsilateral obstruction of the involved and adjacent (double) ureter (7 cases); (3) those with obstruction of both upper urinary tracts, resulting from bilateral ureteroceles (1 case), or resulting from a single ureterocele which gives vesical outlet blockage (4 cases). The wide variety of combinations are shown graphically in Figures 3 and 4. In none of the patients were there ureteral calculi but such a complication has been observed by other surgeons. Innumerable lesion complexes, with all variations in degree, can occur; it is therefore imperative to investigate the entire urinary tract so that a clear picture of the situation is gained before surgical attack is made on an isolated part of the system.

Clinical Picture

As with most congenital anomalies of the genitourinary tract in infants and children, evidences of pyuria is the most common complaint (Table I). In 12 of these cases, the finding of a cloudy urine led to the seeking of medical advice. In 8 others, pus was found on microscopic examination of the urine during routine studies. In only one case was the urine clear.

Next in order of frequency of occurrence are those symptoms suggesting irritation of the bladder.

Dysuria, frequency, enuresis and hesitancy in starting the urinary stream were found in 11 of the patients. Urgency, hesitancy, dribbling and inability to void (suggesting intermittent or continuous bladder-outlet obstruction) were observed in 4 cases. In 2 males, a 9 day old baby and a 2 mos. old infant, these symptoms were coupled with a history of lower abdominal distention, presumably from an over-filled bladder. In 2 older patients the obstructive episodes were intermittent and not associated with prominence of the bladder but on catheterization both carried residual urines of over 50 cc.

In a third of the subjects there was fever, the cause for which was found only after appropriate examination and studies. Hematuria occurred in 2 cases. One child was brought to the hospital primarily because a mass (ureterocele) protruded from the urethra.

These children seem to have less pain than is often the case with obstructions high in the urinary tract. It appears to be present in less than a third of them and was the chief complaint in only one.

TABLE I

SYMPTOMS AND SIGNS IN 21 PATIENTS WITH URETEROCELES

	Present in	Chief complaint in
Cloudy urine (pyuria)	20	12
Vesical irritation	11	4
Fever	7	0
Recurrent abdominal pain	6	1
Vomiting	5	0
Urgency and hesitancy suggesting bladder-neck obstruction	4	1
Failure to gain wt.	3	1
Hematuria	2	1
"Cyst" presenting from urethra (in female)	2	1

Of course, the young age of many of these subjects makes it impossible to give any accurate statement regarding the actual frequency with which abdominal pain occurred.

Physical examination is usually of little help in establishing the correct diagnosis, except when there is flank tenderness from an active pyelonephrosis or when there is a palpable mass in the lower abdomen which represents a distended bladder as a result of vesical-neck obstruction. In only rare instances is it possible by rectal examination to palpate a mass in the region of the bladder floor, which may be either a distended ureter or a ureterocele itself.

Examination of the urine shows varying degrees of pyuria and albuminuria in most instances. Casts are rarely found. The nonprotein nitrogen level in the blood is significantly elevated in only rare instances. Cultures of the urine in 19 of these cases showed a bacilluria due to B. coli, Staphylococcus, Streptococcus fecalis, B. pyocyaneus, or Friedlander's bacillus.

To aid in the recognition of a ureterocele, several simple procedures are available. By careful roentgenographic investigation, the correct diagnosis was made in 10 of the 21 cases without cystoscopy. The intravenous pyelogram was diagnostic in 6 instances; suitable films showed hydroureter and hydronephrosis (Fig. 5) in association with an ipsilateral translucent filling defect in the dye-filled bladder shadow. In a few instances, the ballooned-out and dye-filled ureterocele is more opaque than the bladder shadow, and certainly the intense and continued opacification of a ureter, particularly when this is dilated, should make one suspect obstruction at its lower end (Fig. 6). A cystogram should be made on any patient whose pyelogram suggests low ureteral or uretero-vesical obstruction. By moderately distending a bladder with 4% sodium iodide solution, a filling defect such as that made by a distended ureterocele can often be demonstrated (Fig. 7).

Cystoscopy is not required in all cases but generally it is desirable to confirm the diagnosis which has been already made by roentgenographic means or to establish the diagnosis when other types of examination have failed to clearly indicate the nature of the pathology which is present. When a ureterocele is large it may press directly against the cystoscope and thereby shut off a view of the bladder interior. Ureteroceles of small or moderate size can be seen as domed-shaped swellings replacing one side of the bladder trigone, the mass projecting into the bladder and being surmounted

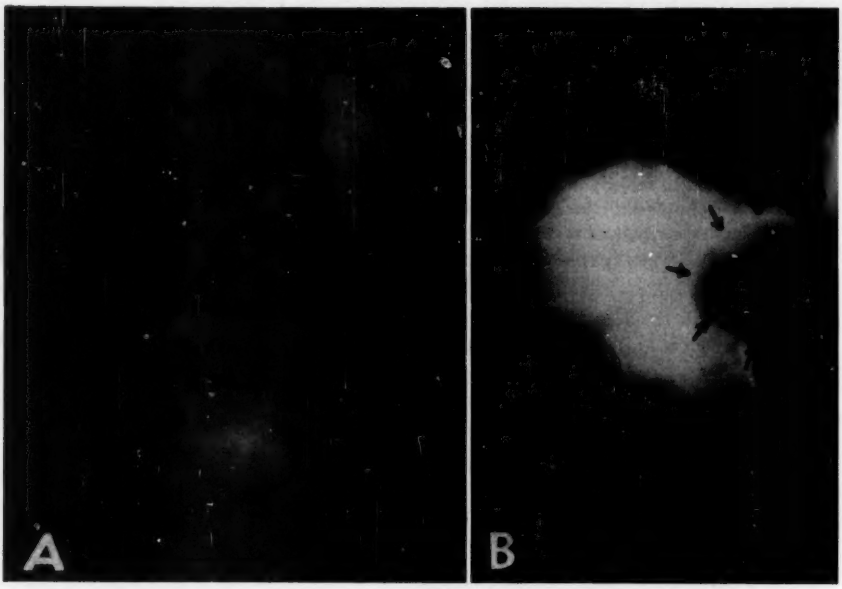

FIG. 5. A. Intravenous pyelogram from child with left sided ureterocele and resultant marked hydronephrosis on same side. B. Cystogram from same patient showing large filling defect (indicated by arrows) made by ureterocele which projects into bladder lumen.

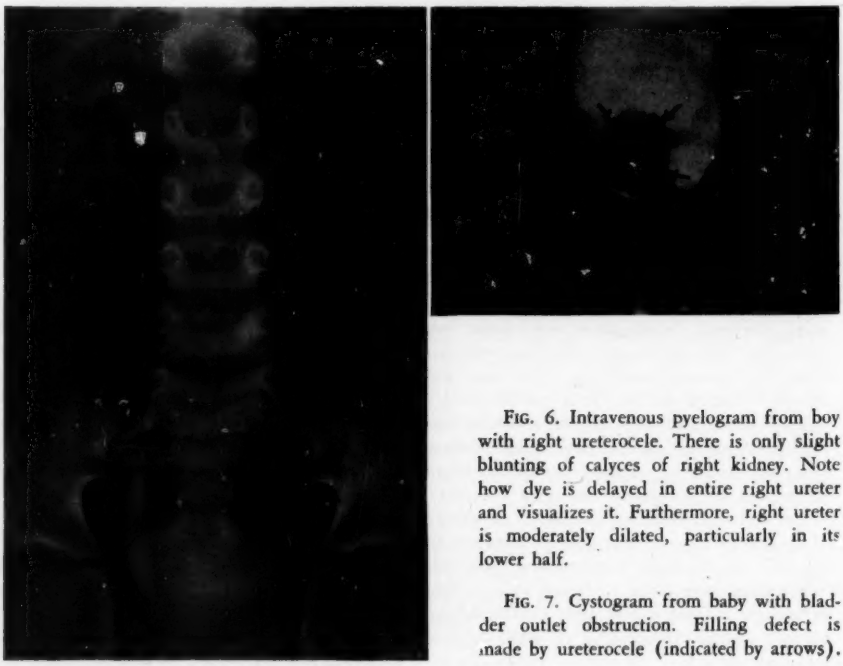

FIG. 6. Intravenous pyelogram from boy with right ureterocele. There is only slight blunting of calyces of right kidney. Note how dye is delayed in entire right ureter and visualizes it. Furthermore, right ureter is moderately dilated, particularly in its lower half.

FIG. 7. Cystogram from baby with bladder outlet obstruction. Filling defect is made by ureterocele (indicated by arrows).

by a stenotic ureteral orifice. The tiny opening will rarely allow a catheter to be passed up the ureter. Occasionally, the "cyst" appears to vary in size and tension as some urine escapes from it or as the sac has transmitted to it the rhythmic peristaltic contractions of the ureteral system.

Treatment

As with most obstructive uropathies in infants and children, a conservative attitude towards definitive treatment is preferable. One is loath to deprive a growing child of renal tissue which is not irreparably damaged; for this reason radical surgery in these cases was limited to 1 nephrectomy and 1 heminephrectomy. The remaining 19 patients were handled by some direct attack on the ureterocele, the removal of which or the incision of which allowed an adequate flow of urine, gave a reasonable chance of combating the infection (with or without chemotherapy), and at the same time made it possible to save whatever kidney substance was present.

In choosing a method of operative approach to an intravesical ureterocele, one should be guided by the age and sex of the patient, the availability of specialized instruments and the training and ability of the surgeon. While urologists have been eminently successful in treating ureteroceles in older children or adults by a transurethral approach for incising a ureterocele with cystoscopic scissors or puncturing it with an endothermy instrument, it is the authors' firm conviction that for infants and small children it is far safer and more effective to treat these lesions through a suprapubic opening of the bladder. Under this direct vision and handling, the ureterocele can be quickly and easily treated. It is believed that in infants and small children, particularly males, this is the approach of choice and for most surgeons it is less hazardous than cystoscopic manipulation.

Simple dilatation of a small ureterocele opening, even when it is done under direct vision through an open bladder, gives disappointing end-results; the authors have always had to follow it with some other form of treatment and have therefore abandoned this form of therapy which theoretically might seem to be adequate.

Great stress must be given to the fact that excision of a ureterocele—in part or in toto—is not only unnecessary but is distinctly harmful. The removal of any tissue will obviously relieve existing ureteral obstruction, but it is apt to produce an incompetence of the uretero-vesical valve mechanism. Excision of tissue allows a reflux of bladder urine up into the ureter, an increasing hydronephrosis and a continuing pyronephrosis—all of which contribute to progressive renal damage. The authors have performed operations for "uncapping" ureteroceles and also more extensive resections wherein the entire mass was removed; follow-up studies give indubitable evidence that the over-all results have been extremely poor. Cystogram studies some months or years later have shown reflux of urine on the operated side, the urines have long continued to be filled with pus, and there has been progressive loss of renal function on the affected side. In 2 instances, secondary operations have been performed to reimplant the ureter through the bladder wall in a manner to re-establish some valve-like action. Studies of these operations have led us to the conclusion that "excision" of ureteroceles should be abandoned.

Without question, the treatment of choice is the simple vertical incision of the dome of the ureterocele, making a slit-like enlargement of the existing ureteric orifice. The length of such incision should vary from 2 to a maximum of 4 mm., depending upon the over-all size of the ureterocele, having in mind that the larger masses will shrink more as they collapse and hence any slit in them will shorten more than is the case with small ureteroceles. No attempt should be made to suture the membrane of the ureter to that of the bladder. To promote a thorough flushing out of the urinary tract, a mushroom suprapubic catheter should be left in place and kept open for 7 or 8 days. The bulbous end of this should be placed high in the bladder so that it does not rest against the trigone and cause undue discomfort. Furthermore, the catheter should be led obliquely upward through the abdominal wall, a direction which facilitates rapid and spontaneous closure of its sinus when the catheter is withdrawn. In all cases wherein simple incision of a ureterocele has been performed, the follow-up studies have shown an excellent result.

As an adjunct to the surgical treatment of each patient, pyuria should be intensively treated with the best available chemotherapeutic agent. After determining the type of organism which is present in the urine, that drug is selected which is most apt to achieve sterilization. Penicillin, sulfadiazine, streptomycin or aureomycin are given in appropriate doses and are continued until a few days after withdrawal of the suprapubic tube. It is rarely necessary to continue these drugs for a longer period.

It is hardly necessary to point out that infection cannot be satisfactorily or permanently eradicated unless the mechanical obstruction has been completely relieved.

Upon reviewing the cases and tabulating the success or failure which followed various surgical procedures, it becomes quite clear that achievement of uniformly satisfactory results depends upon the accomplishment of 3 things: (1) relief of the obstruction; (2) control of the infection; (3) avoidance of any operative procedure which destroys the uretero-vesical valve and permits urinary reflux. Remarkable restorative powers in the ureters and kidneys of children have been observed provided stasis, obstruction and infection are controlled and provided that reflux does not occur. The simplest possible correction—that of making a small slit in the wall of the ureterocele—will relieve the obstruction and will permit a satisfactory flow of urine but will not jeopardize the chances of a successful result because it does not incur a loss of the uretero-vesical valve. In infants and most children, this incision of a ureterocele is best made under direct vision, working through a suprapubic cystotomy.

Summary

Ureteroceles are abnormalities which result from congenital stenosis of a uretero-vesical junction. That portion of the ureter which obliquely traverses the bladder wall becomes ballooned out so that it projects into the lumen of the bladder. This bulging mass in the bladder may be one to several centimeters in diameter. The lesions are more common in females. The outstanding symptoms are referable to pyuria, which appears in most cases. There may be abdominal or flank pain from the ureteric obstruction. In some patients the ureterocele may lodge in the bladder outlet and block the urinary flow from the entire urinary tract, in this way giving rise to damage in both kidneys. In rare instances a ureterocele may prolapse through the urethra of the female. Ureteroceles are apt to give rise to symptoms in infancy or childhood, but in some cases they are not manifest until later years. Intravenous pyelography and cystography will often give conclusive evidence of the presence of the abnormality, but in some patients cystoscopy will be necessary to establish the diagnosis.

Ureteroceles are not difficult to treat. They should never be excised, because such surgical attack is apt to destroy the uretero-vesical valve and permit reflux of urine from the bladder to the upper urinary tract, a complication which results in increasing hydronephrosis and pyelonephritis. A ureterocele mass will collapse by merely incising its dome in a longitudinal manner for a distance of 2 to 4 mm. This effectively relieves the ureteral obstruction and is the most important step in the therapy of any existing urinary infection. Chemotherapy is a valuable adjunct in the treatment of pyuria, but will have permanent benefit only if the mechanical obstruction has been completely eradicated. In babies and small children it is preferable to avoid incision of a ureterocele by cystoscopic instrumentation; it is safer to open the bladder and incise the structure under direct vision. The results of this latter type of therapy are extremely gratifying and in most instances such conservative measures will permit saving of the kidney on the affected side.

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SPANISH ABSTRACT

Ureterocele en la Infancia y la Niñez

Los ureteroceles son anormalidades que resultan de estenosis congénita de una conexión ureterovesical. Esa porción del uréter que oblicuamente atraviesa la pared de la vejiga se infla de manera que proyecta en el lumen de la vejiga. Esta masa pandeada en la vejiga puede llegar a tener de uno a varios centímetros de diametro. Las lesiones son más comunes en las hombras. Los síntomas sobresalientes tienen referencia a la piuria, que aparece en la mayor parte de los casos. Pueda ser que haya dolor abdominal o en el flanco a causa de la obstrucción uretérica. En algunos pacientes el ureterocele puede alojarse a la salida de la vejiga y obstruir la corriente de orina de toda la vía urinaria, dañando de esta manera ambos riñones. En raros casos un ureterocele prolapsa a través de la uretra de la mujer. Los ureteroceles pueden originar síntomas en la infancia o en la niñez, pero en algunos casos no se manifiestan hasta años más tarde. La pielografía y cistografía intravenosa a menudo dan prueba conclusiva de la presencia de la anormalidad, pero en algunos pacientes la cistocopía será necesaria para establecer la diagnosis.

No es difícil tratar ureteroceles. Nucan deben de ser excindidos porque esta operación quirúrgica está apta a destruir la válvula uretero-vestical y permitir el reflujo de orina de la vejiga al canal urinario superior, una complicación que resulta en hidronefrosis y filonefritis. Una masa de ureterocele se retractará con solo hacer una incisión longitudinal de 5 a 10 mm. en la cúpula. Esta alivia eficazmente la obstrucción ureteral y es el paso más importante en la terapia de cualquier infección urinaria que existe. La quimiterapia es una ayuda de gran valor en el tratamiento de la piuria, pero será de provecho permanente solamente si la obstrucción mecánica ha sido completamente desarraigada. En bebés y niños pequeños es preferible evitar la incisión de un ureterocele mediante instrumentación cistoscópica, es más seguro abrir la vejiga y hacer la incisión en la estructura bajo visión directa. Los resultados de este último tipo de terapia son extremadamente satisfactorios y en la mayor parte de los casos estas medidas conservativas permitirán la salvación del riñón en el lado afectado.

300 Longwood Avenue

EXPERIMENTAL BASIS FOR PREDICTION OF THERAPEUTIC EFFICACY OF STREPTOMYCIN IN INFECTIONS CAUSED BY GRAM NEGATIVE BACILLI

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WHILE streptomycin has proved of great value in the treatment of infections caused by gram negative bacilli it differs markedly in its therapeutic efficacy among them. Emergence of resistance of the infecting agent has been shown to limit the value of streptomycin in this group of infections; in eight different species the cells responsible for a high degree of this phenomenon have been shown to arise as the result of bacterial mutation.[1-5] It was possible to demonstrate the presence of mutants resistant to streptomycin 1000 μg./cc. in large populations of H. influenzae, H. pertussis, H. parapertussis, E. coli, Salmonella, Shigella, S. typhosa and Ps. aeruginosa. However, the frequency of occurrence of the highly resistant mutants of these species showed no correlation with the therapeutic efficacy of streptomycin.

This paper presents the results of investigation of the causes of the differences in therapeutic success of streptomycin among infections with the above organisms. Two factors have been studied for this purpose: (1) frequency of occurrence of their mutants exhibiting lower degrees of resistance to streptomycin; (2) speed of the lethal action of streptomycin on their sensitive cells.

MATERIAL AND METHODS

Cultures: All organisms studied were dried and sealed under vacuum[6] within a few days of cultivation from patients with acute infections.

Rate of Occurrence of Resistant Mutants: In each of the 8 species, cells which on first contact with streptomycin formed colonies in media containing streptomycin 25 and 100 μg./cc. were studied for the frequency of their occurrence. The procedures used for examining H. influenzae, E. coli, H. pertussis and Shigella were the same as those described for study of frequency of mutants resistant to 1000 μg./cc.[1, 4, 5] Two modifications were necessary in studying Salmonella, S. typhosa, Ps. aeruginosa and H. parapertussis. An even smaller initial inoculum was required to ensure that the resistant colonies growing in the pour plates containing streptomycin represent new mutants and not those resulting from reproduction of resistant cells present in the broth culture used for seeding. To use the formula of Luria and Delbrück[7] for estimating mutation rate the data must be derived from experiments in which the resistant colonies growing in pour plates containing streptomycin 25 and 100 μg./cc. cannot originate from reproduction of those already present in the broth inoculum used for production of independent cultures. The size of the inoculum suitable for this purpose varied with the organism and the concentration of streptomycin. For determining mutation rate of cells resistant to 25 μg./cc. the seeding broth (culture in neopeptone broth incubated 16 to 18 hrs.) was diluted 10^{-5} or 10^{-6} and for those resisting 100 μg./cc. a dilution of 10^{-3} or 10^{-4} was adequate. For 3 of these organisms—Salmonella, S. typhosa and Ps. aeruginosa—the independent cultures were grown in 4.5 cc. quantities of neopeptone broth to which 0.5 cc. quantities of the above dilutions of

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inoculum were added. The prevalence of resistant mutants in the seeding broth was determined by inoculation of each of 3 pour plates with 100 times the number of organisms used for producing independent cultures. The H. parapertussis seeding suspensions were prepared as follows: part of the growth (about ¼) on a Bordet-Gengou[8] plate after 24 hrs.' incubation is suspended in 5 cc. of neopeptone broth to obtain a turbidity corresponding to a reading of 150 on the Klett-Summerson photoelectric colorimeter (#54 filter); appropriate dilutions are seeded in 0.5 cc. quantities on each of 10 petri dishes of Bordet-Gengou agar which are used for the independent cultures.

The streptomycin-containing media used for these experiments varied with the organisms: Levinthal media[1] broth and agar for H. influenzae, proteose #3 agar (Difco) and neopeptone broth[9] for enteric organisms and Bordet-Gengou agar for H. pertussis and H. parapertussis. The frequency of occurrence of mutants resisting streptomycin 25 and 100 μg./cc. was determined from the same independent cultures in the cases of H. influenzae, H. parapertussis, E. coli and Shigella.

Speed of Lethal Action on Sensitive Cells: Three different types of media were used to cultivate the 8 species from the dried state: Levinthal broth for H. influenzae, neopeptone broth for E. coli, Salmonella, S. typhosa, Shigella and Ps. aeruginosa and Bordet-Gengou medium for H. pertussis and H. parapertussis.

The procedure used was identical for the 1st 6 of the above species. After cultivation in fluid media from the dried state for 16 to 18 hrs. the culture was diluted at 10-fold steps to 10^{-7}; the last dilution was used for determining the number of viable bacteria. A dilution of 10^{-4} was added in 0.5 cc. amounts to 4.5 cc. quantities of appropriate broth, one of which contained streptomycin 11 μg./cc., one 110 μg./cc. and one no streptomycin; the dilution by addition of inoculum resulted in approximately 10 and 100 μg./cc. concentrations, respectively. This procedure exposed populations of approximately 10,000 organisms/cc. to each concentration of streptomycin in an environment which permitted growth. Incubation was carried out at 37° C., and at intervals of 0.5, 1, 2, 4, 6 and 24 hrs. a sample was removed, diluted to 10^{-1}, 10^{-2} and 10^{-3} and a 0.5 cc. sample of each as well as the undiluted broth culture was seeded into a pour plate preparation in suitable agar. After 48 hrs.' incubation the colonies were counted. When suspensions of organisms contained concentrations of streptomycin sufficient to inhibit growth when seeded in the pour plate preparation, 2 appropriate measures were taken to remove this effect: for samples cultured after 30 min.' incubation, simple dilution was used; specimens which had been exposed to streptomycin during incubation for 1 hr. or more were centrifuged and resuspended in broth before being mixed with agar for pouring.

For studying the action of streptomycin on sensitive cells of H. pertussis and H. parapertussis, the growth on the surface of a Bordet-Gengou plate was harvested after 24 hrs.' incubation at 37° C. by suspending in neopeptone broth; this was adjusted to a turbidity of 80 to 85 on the Klett-Summerson photoelectric colorimeter. The latter suspension was diluted 10^{-4} in neopeptone broth and seeded in 0.5 cc. quantities into 4.5 cc. of modified Cohen medium.[10]* From this point the procedure was the same as that described above for the other organisms with 1 exception: the pour plates used for identifying viable organisms were incubated for 6 days before the number of colonies were recorded. Here, too, the procedure aimed to test populations of approximately 10,000 organisms/cc.

Experimental

Examination of Eight Species for Cells Resistant to Streptomycin 25 and 100 μg./cc.

The mutation rates of cells resistant to streptomycin 1000 μg./cc. have been reported for each of the 8 species under investigation.[1, 2, 4, 6] From these results it is apparent that differences in the frequencies of their highly resistant mutants do not explain the variation in therapeutic efficacy of streptomycin among these infections since there are no significant differences among the rates of the 8 species.

Our experience with routine sensitivity tests suggested that the rate of occurrence of variant cells possessing a lower degree of resistance, for example, to 25 and 100 μg./cc., might offer an explanation. Accordingly all 8 species were examined to determine whether organisms capable of growth in these concentrations of streptomycin are present in large populations prior to exposure to streptomycin and whether they also exhibit the characteristics of mutants and how frequently they occur. It has been demonstrated that the organisms which on first contact with streptomycin form colonies in media containing 25 or 100 μg./cc. can be found in populations of each of these species prior to

* Modification—25% fresh horse plasma substituted for yeast dialysate.

TABLE I

RANDOM DISTRIBUTION OF CELLS RESISTANT TO STREPTOMYCIN 25 μg./cc. AMONG 10 INDEPENDENT POPULATIONS OF EQUAL SIZE

Species	Source	Total bacteria cultured	Resistant colonies formed in agar containing streptomycin 25 μg./cc.	
			Total resistant colonies	Distribution of colonies among plates
H. influenzae	Pool	1.2×10^{11}	38	7-5-6-6-14
	Indep't	2.5×10^{11}	80	45-10-5-0-3-9-0-7-1-0
H. pertussis	Pool	1.8×10^{10}	19	1-5-3-3-7
	Indep't	3.7×10^{10}	62	0-0-30-6-21-1-0-2-1-1
E. coli	Pool	1.8×10^{10}	36	11-6-8-4-7
	Indep't	3.7×10^{10}	87	9-5-8-3-3-5-23-18-5-8
Shigellae	Pool	2.4×10^{10}	29	7-5-7-5-5
	Indep't	4.8×10^{10}	64	50-1-0-2-1-2-3-4-0-1
H. parapertussis	Pool	9.5×10^{6}	73	15-21-14-14-9
	Indep't	1.9×10^{7}	170	0-3-0-148-0-14-4-1-0-0
Salmonellae	Pool	3.9×10^{6}	72	9-15-19-13-16
	Indep't	7.8×10^{6}	125	0-0-37-1-0-0-45-2-25-15
S. typhosa	Pool	9.5×10^{5}	86	11-14-20-17-24
	Indep't	1.9×10^{6}	172	3-2-160-1-3-1-1-1-0-0
Ps. aeruginosa	Pool	7.0×10^{5}	28	4-6-6-6-6
	Indep't	1.4×10^{6}	48	2-6-5-3-0-0-6-11-8-7

Indep't = Independent.

exposure to streptomycin; they also exhibit the characteristics of mutants already described for the highly resistant mutants.

Demonstration of Traits Characteristic of Mutants: Each of the 8 species was examined to determine whether its colonies growing in the presence of streptomycin 25 or 100 μg./cc. exhibited 3 traits characteristic of mutants: (1) a continuous irregular occurrence resulting in different prevalence in independent cultures of same strain and population size; (2) transmission of resistance, unchanged in degree, through many generations in the absence of streptomycin; (3) a rate of occurrence consistent with mutation frequency and not varying significantly among different strains of the same species.

The procedures used have already been reported.[1, 4, 5] The modifications used in determining the mutation rates of less resistant mutants are described under *Material and Methods*.

1. Random distribution of resistant cells: Table I lists the results of experiments which demonstrate for each of the 8 species the random occurrence of cells which resist the action of streptomycin 25 μg./cc. and Table II, similar data on cells resistant to streptomycin 100 μg./cc. Even though the population sizes per plate are equal in the 2 series the distribution of resistant colonies among the plates, each of which was seeded from a different independent culture, is irregular compared to the relatively even distribution among those inoculated from a single source, the pool. These data preclude the development of resistance as a result of interaction between the bacteria and streptomycin and offer evidence for spontaneous occurrence of resistant cells consistent with mutational origin.

TABLE II

RANDOM DISTRIBUTION OF CELLS RESISTANT TO STREPTOMYCIN 100 μg./cc. AMONG 10 INDEPENDENT POPULATIONS OF EQUAL SIZE

Species	Source	Total bacteria cultured	Resistant colonies formed in agar containing streptomycin 100 μg./cc.	
			Total resistant colonies	Distribution of colonies among plates
H. influenzae	Pool	1.2×10^{11}	23	3-9-5-2-4
	Indep't	2.5×10^{11}	59	43-3-3-0-1-4-2-1-2-0
H. pertussis	Pool	8.4×10^{10}	19	4-3-2-7-3
	Indep't	1.7×10^{11}	32	7-1-0-0-4-7-0-2-0-11
E. coli	Pool	1.8×10^{10}	84	20-17-19-18-10
	Indep't	3.7×10^{10}	148	20-15-13-9-13-15-46-9-2-6
Shigellae	Pool	2.4×10^{10}	40	5-8-9-10-8
	Indep't	4.8×10^{10}	74	55-0-0-6-4-0-3-1-4-1
H. parapertussis	Pool	1.0×10^{8}	77	15-16-12-20-14
	Indep't	2.0×10^{8}	211	2-0-172-0-33-0-0-0-0-4
Salmonellae	Pool	1.0×10^{9}	29	5-5-3-10-6
	Indep't	2.0×10^{9}	49	0-28-0-0-0-8-0-7-5-1
S. typhosa	Pool	1.6×10^{9}	185	41-41-33-45-25
	Indep't	3.2×10^{9}	310	0-12-0-0-0-282-7-7-2-0
Ps. aeruginosa	Pool	7.0×10^{7}	54	9-10-9-14-12
	Indep't	1.4×10^{8}	68	15-3-8-5-6-2-2-8-5-14

Indep't = Independent.

2. Inheritance of the resistant trait: To study the inheritance of resistance to streptomycin 25 and 100 μg./cc., 2 resistant colonies of each of the 8 species were subcultured 20 times at 6 to 48 hr. intervals in the absence of streptomycin. The degree of resistance of their progeny was retested after 1, 10 and 20 subcultures by seeding an equal number of organisms into each of 2 pour plate preparations of appropriate agar, 1 with streptomycin and 1 without; colonies growing in these 2 environments were counted. Only colonies growing equally well initially in the presence and absence of streptomycin of the concentration under examination were selected for this study. Tables III and IV present the results. It is seen that the number of colonies growing in the absence and presence of streptomycin continued to be essentially the same after each of these intervals with certain exceptions.

3. Rate of occurrence: The frequency of occurrence of cells resistant to streptomycin 25 and 100 μg./cc. is listed in Tables V and VI for 2 strains of each of the 8 species; these rates are consistent with mutational origin. The values for the rates expressed in terms of per bacterium per bacterial generation are listed in the last column; they have been calculated from the data listed by the method of Luria and Delbrück.[7] The random occurrence of resistant colonies among independent cultures of the same strain and population size is apparent. The details of application for estimating the mutation rate of highly resistant mutants of H. influenzae have been reported.[1] These data also provide evidence that the colonies are derived from new resistant cells and not from the progeny of those seeded from the inoculum.

It is apparent from the results of the experiments which were examined for evidence of the

TABLE III

TRANSMISSIBILITY OF DEGREE OF RESISTANCE IN ABSENCE OF STREPTOMYCIN IN PROGENY OF COLONIES FORMED IN AGAR CONTAINING STREPTOMYCIN 25 μg./cc.

Species	Colony number	Number of colonies which grew from equal inocula in absence of streptomycin and in presence of streptomycin 25 μg./cc. after subcultures indicated					
		1		11		20	
		0*	25 μg.	0	25 μg.	0	25 μg.
H. influenzae	1	152	158	188	176	230	258
	2	146	132	130	138	184	192
H. pertussis	1	300	302	156	149	248	260
	2	110	100	105	100	240	286
E. coli	1	216	198	120	122	134	124
	2	188	166	132	0	98	0
Shigellae	1	44	68	100	94	54	64
	2	50	74	90	92	78	68
H. parapertussis	1	900	930	111	80	828	742
	2	800	850	221	163	560	528
Salmonellae	1	234	216	62	52	132	74
	2	286	276	84	20	138	14
S. typhosa	1	230	206	116	112	82	72
	2	392	348	252	290	146	132
Ps. aeruginosa	1	140	134	56	2	100	0
	2	136	138	226	0	52	0

* Absence of streptomycin.

3 above characteristics that cells resistant to streptomycin 25 or 100 μg./cc. also arise as the result of bacterial mutation.

Correlation of Frequency of Resistant Mutants and Speed of Lethal Action on Sensitive Cells with Therapeutic Efficacy of Streptomycin

1. Mutation rate of resistant cells: In Table VII is listed for each 1 of these species the frequency of occurrence of mutants with these lower degrees of resistance and for comparison the incidence of those capable of growth in streptomycin 1000 μg./cc. It is seen that in the case of H. influenzae the rate of occurrence of mutants which resist the action of streptomycin 25 or 100 μg./cc. is not different from the frequency of those which grow in streptomycin 1000 μg./cc. The same is true of H. pertussis, E. coli and Shigella. However, the situation is quite different for Salmonella, S. typhosa, H. parapertussis and Ps. aeruginosa. Mutants of these organisms growing in streptomycin 100 μg./cc. occur 100 times more frequently than those resisting 1000 μg./cc. and those surviving in 25 μg./cc. are 10,000 to 100,000 times more frequent. In other words, mutants of H. influenzae, H. pertussis, E. coli and Shigella which resist the action of streptomycin 25 and 100 μg./cc., but are sensitive to 1000 μg./cc., are so rare that they probably play an unimportant role in therapeutic failure of streptomycin. However, the much greater frequency of mutants with these degrees of resistance in

the other 4 species suggests that they play an important part in the emergence of resistance of these organisms to streptomycin and in the consequent therapeutic failure.

2. Rapidity of lethal action: For the purpose of determining rapidity of lethal action of streptomycin on the sensitive members of these species, a population of approximately 10,000 organisms was exposed to 2 different concentrations of streptomycin—10 and 100 μg./cc.—for varying lengths of time; at intervals the number of viable organisms per cc. was determined.

Chart 1 presents the action of streptomycin 10 μg./cc. on a small population of each of the 8 species. This concentration is lethal for 100% of H. influenzae in 6 hrs.; in 2 hrs. 99.99% are killed. For E. coli a 6 hr. exposure is required to kill all cells and for Shigella 4 hrs. H. pertussis is completely eliminated in less than 24 hrs.; 99% are killed in 6 hrs. in all experiments. Three species, on

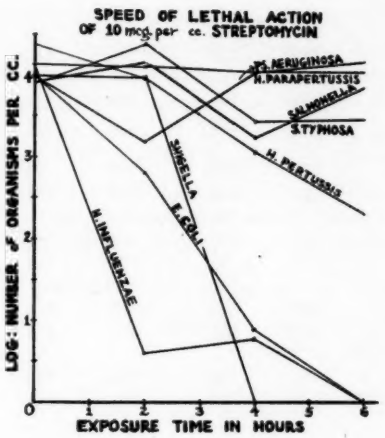

CHART 1

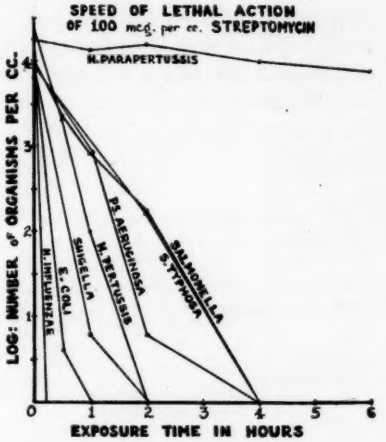

CHART 2

the other hand—Salmonella, S. typhosa and Ps. aeruginosa—while they show some decrease in their numbers in 6 hrs., have increased 24 hrs. after exposure to a number comparable with the control. H. parapertussis is not reduced significantly in 6 hrs., and after 24 hrs. the population shows an increase. The variation in results of different experiments is summarized in Table VII.

Chart 2 demonstrates that a concentration of streptomycin 100 μg./cc. exerts a more rapid lethal action on all species. For H. influenzae exposure for 10 min. is adequate for death of all organisms, for E. coli 1 hr., for Shigella 2 hrs. and for H. pertussis 2 hrs. A lethal effect on 100% of Salmonella, S. typhosa and Ps. aeruginosa occurs at 4 hrs. The H. parapertussis population is not significantly decreased after exposure for 6 hrs., and a small fraction is viable after 24 hrs. However, it must be emphasized that this concentration, 100 μg./cc., can be obtained only in the urine and spinal fluid without serious injury to the patient from streptomycin. A summary of the variation seen in different experiments is listed in Table VII.

Correlation with Therapeutic Efficacy of Streptomycin: The relationship of these 2 factors, mutation frequency of resistant cells and speed of lethal action on sensitive cells, to therapeutic efficacy of streptomycin in infections due to these organisms is suggested by the order of listing of organisms in Table VII. These data suggest that the organisms causing infections which are successfully treated with streptomycin—as, for example, H. influenzae, E. coli and H. pertussis—have also a low incidence of mutants which resist the action of streptomycin 25 and 100 μg./cc. In addition, their sensitive cells are killed rapidly by concentrations of streptomycin safely maintained in body fluids. On the other hand, in those infections in which streptomycin has not been found effective therapeutically a concentration of 10 μg./cc. is not primarily bactericidal for the sensitive cells, and the frequency of mutants resistant to streptomycin 25 μg./cc. is relatively high.

TABLE IV

TRANSMISSIBILITY OF DEGREE OF RESISTANCE IN ABSENCE OF STREPTOMYCIN IN PROGENY OF COLONIES FORMED IN AGAR CONTAINING STREPTOMYCIN 100 μg./cc.

Species	Colony number	Number of colonies which grew from equal inocula in absence of streptomycin and in presence of streptomycin 100 μg./cc. after subcultures indicated					
		1		11		20	
		0*	100 μg.	0	100 μg.	0	100 μg.
H. influenzae	1	178	162	162	188	98	108
	2	112	96	196	170	120	146
H. pertussis	1	46	112	194	194	240	246
	2	282	274	312	248	252	208
E. coli	1	140	170	130	142	104	94
	2	182	148	122	120	176	194
Shigellae	1	80	74	102	120	102	82
	2	126	112	52	56	98	92
H. parapertussis	1	260	280	340	374	480	416
	2	214	244	400	368	490	512
Salmonellae	1	306	304	140	60	176	120
	2	126	140	178	72	158	154
S. typhosa	1	192	70	106	48	86	30
	2	234	54	114	52	102	68
Ps. aeruginosa	1	476	340	40	2	58	6
	2	84	72	42	36	134	48

* Absence of streptomycin.

DISCUSSION

The data presented suggest that the therapeutic efficacy of streptomycin among infections caused by gram negative bacilli is closely correlated with the two factors studied: the frequency of cells resistant to streptomycin 25 or 100 μg./cc., and the speed of its lethal action on the sensitive cells.

It is apparent that the colonies forming in streptomycin 25 μg./cc. represent the sum of those which can grow in 25, 100 and 1000 μg./cc. However, only in experiments on H. influenzae, H. pertussis and E. coli were the populations examined large enough to contain a significant number of mutants resistant to 100 or 1000 μg./cc. It has been reported for H. influenzae that cells resistant to 100 μg./cc. are uniformly resistant to 1000 μg./cc.;[1] it is seen from Table VII that there is no significant difference in frequency of occurrence of colonies forming in 25, 100 and 1000 μg./cc. Therefore the mutation rate of cells resistant to 25 μg./cc. and sensitive to 100 and 1000 μg./cc. must be much lower than those with a higher degree of resistance. That they do occur in H. influenzae cultures is shown by the results in Table VIII. Of 28 colonies forming in medium

containing streptomycin 25 μg./cc. only 20 grew in 100 μg./cc. Three of the 20 colonies which grew on medium containing streptomycin 100 μg./cc. failed to grow on 1000 μg./cc. This raises the question of the existence of mutants resistant to 100 μg./cc. but not to streptomycin 1000 μg./cc.; in our experience they occur so rarely that they are difficult to demonstrate.

In populations of Salmonella, S. typhosa, Ps. aeruginosa and H. parapertussis the situation is quite different. The cells which form colonies in the presence of streptomycin 25 μg./cc. occur at a much higher rate, 10,000 to 100,000 times more frequently than those resistant to 1000 μg./cc. and those which grow in streptomycin 100 μg./cc. occur about 100 times more frequently than those which grow in 1000 μg./cc. There is reason to believe that most of the mutants growing at these different levels of streptomycin vary in their metabolic needs at least quantitatively as expressed by their varying capacity to grow in different concentrations of streptomycin. These facts are shown in Table VIII which lists the results of examination for the degree of resistance exhibited by a representative sample of colonies forming in medium containing streptomycin 25 and 100 μg./cc. It should be pointed out that the use of small populations for studying cells resistant to 25 μg./cc. (made possible by their high mutation rate) is probably responsible for absence of mutants resistant to 1000 μg./cc. and for there being only a small fraction of the total colonies resistant to 100 μg./cc.

TABLE V

EXPERIMENTAL DATA USED FOR DETERMINING MUTATION RATES AT 25 μg. OF STREPTOMYCIN PER CC.

Species	Strain	Inoculum Used for Seeding 10 Independent Cultures			10 Independent Cultures Examined for Resistant Colonies			
		Prevalence resistant colonies	Dilution used	Total cells seeded	Average no. cells per sample	Average no. resistant colonies per sample	Number resistant colonies per plate	Mutation rate
H. influenzae	1	$1:9.8\times10^{9}$	none	1.2×10^{10}	2.5×10^{10}	3.1	4-1-0-2-7-0-5-9-0-3	5.1×10^{-11}
	2	$1:3.4\times10^{9}$	none	1.7×10^{9}	1.0×10^{10}	1.2	1-2-1-3-2-0-0-1-2-0	6.6×10^{-11}
H. pertussis	1	$1:2.6\times10^{10}$	5×10^{-1}	1.0×10^{9}	1.0×10^{10}	1.3	0-1-4-0-0-0-2-0-4-2	6.8×10^{-11}
	2	$0:3.6\times10^{9}$	5×10^{-1}	1.4×10^{8}	3.6×10^{9}	6.2	0-0-30-6-21-1-0-2-1-1	5.8×10^{-10}
E. coli	1	$1:4.9\times10^{8}$	10^{-1}	1.1×10^{9}	1.2×10^{10}	19.3	23-15-18-15-17-11-44-17-13-20	3.8×10^{-10}
	2	$1:1.2\times10^{9}$	10^{-3}	5.9×10^{6}	3.7×10^{9}	8.7	9-5-8-3-3-5-23-18-5-8	7.2×10^{-10}
Shigellae	1	$1:3.6\times10^{7}$	10^{-2}	4.9×10^{7}	4.8×10^{9}	6.4	50-1-0-2-1-2-3-4-0-1	4.3×10^{-10}
	2	$1:8.0\times10^{9}$	10^{-2}	2.9×10^{7}	5.4×10^{9}	26.8	1-0-4-0-2-1-253-3-1-3	1.1×10^{-9}
H. parapertussis	1	$1:1.0\times10^{6}$	10^{-5}	3.4×10^{5}	8.6×10^{5}	2.6	0-4-0-0-9-1-3-7-0-2	1.2×10^{-6}
	2	$1:1.1\times10^{6}$	10^{-5}	2.5×10^{5}	1.9×10^{6}	5.8	0-1-8-30-0-0-1-4-14-0	1.0×10^{-6}
Salmonellae	1	$1:2.9\times10^{4}$	10^{-4}	4.8×10^{3}	3.0×10^{6}	9.0	20-6-0-20-8-2-2-14-0-18	9.0×10^{-7}
	2	$1:9.0\times10^{3}$	10^{-4}	6.0×10^{2}	5.2×10^{5}	6.3	8-0-0-41-0-0-0-9-1-4	4.0×10^{-6}
S. typhosa	1	$1:2.1\times10^{2}$	10^{-4}	4.1×10^{3}	1.9×10^{5}	17.2	3-2-160-1-3-1-1-1-0-0	2.2×10^{-5}
	2	$0:1.6\times10^{4}$	10^{-4}	2.6×10^{3}	2.3×10^{5}	3.0	1-2-5-3-1-17-0-0-0-1	5.4×10^{-6}
Ps. aeruginosa	1	$1:1.2\times10^{5}$	10^{-5}	5.8×10^{4}	6.8×10^{5}	21.6	10-8-18-12-72-64-8-5-5-14	7.5×10^{-6}
	2	$1:6.3\times10^{3}$	10^{-4}	1.0×10^{4}	1.4×10^{5}	4.8	2-6-5-3-0-0-6-11-8-7	1.2×10^{-5}

TABLE VI

EXPERIMENTAL DATA USED FOR DETERMINING MUTATION RATES AT 100 μg. OF STREPTOMYCIN PER CC.

Species	Strain	Inoculum Used for Seeding 10 Independent Cultures			10 Independent Cultures Examined for Resistant Colonies			
		Prevalence resistant colonies	Dilution used	Total cells seeded	Average no. cells per sample	Average no. resistant colonies per sample	No. resistant colonies per plate	Mutation rate
H. influenzae	1	$1:8.1\times10^{9}$	none	1.2×10^{10}	2.5×10^{10}	1.6	2-1-0-2-1-2-4-1-0-3	3.2×10^{-11}
	2	$1:6.8\times10^{9}$	none	1.7×10^{9}	1.0×10^{10}	0.9	1-1-1-1-2-0-0-1-2-0	5.8×10^{-11}
H. pertussis	1	$1:3.6\times10^{10}$	5×10^{-1}	1.8×10^{10}	1.5×10^{10}	1.6	4-0-1-1-1-1-4-2-2-0	5.2×10^{-11}
	2	$1:1.4\times10^{10}$	5×10^{-1}	1.4×10^{10}	1.1×10^{10}	5.0	0-3-3-0-0-35-1-1-0-6-1	1.6×10^{-10}
E. coli	1	$1:7.0\times10^{8}$	10^{-3}	3.9×10^{8}	7.3×10^{9}	4.0	3-5-1-2-5-1-11-8-4-0	2.1×10^{-21}
	2	$1:1.2\times10^{9}$	10^{-3}	5.9×10^{8}	3.7×10^{9}	7.3	7-3-3-9-8-8-13-18-3-1	6.0×10^{-10}
Shigellae	1	$1:6.6\times10^{7}$	10^{-2}	4.9×10^{7}	4.8×10^{9}	7.4	55-0-0-6-4-0-3-1-4-1	4.8×10^{-10}
	2	$1:8.0\times10^{8}$	10^{-2}	2.9×10^{7}	5.4×10^{9}	28.8	0-4-3-4-3-2-256-2-8-6	1.2×10^{-9}
H. parapertussis	1	$1:1.3\times10^{8}$	10^{-4}	3.6×10^{8}	2.0×10^{7}	0.4	0-0-0-0-0-4-0-0-0-0	1.7×10^{-8}
	2	$1:8.3\times10^{8}$	10^{-4}	2.5×10^{8}	1.8×10^{7}	2.0	0-0-0-2-1-0-0-0-14-3	5.3×10^{-8}
Salmonellae	1	$1:5.8\times10^{8}$	10^{-4}	4.8×10^{8}	6.0×10^{8}	3.5	0-8-1-1-3-1-9-5-1-6	2.3×10^{-9}
	2	$1:3.6\times10^{8}$	10^{-4}	6.0×10^{8}	2.0×10^{8}	4.9	0-28-0-0-0-8-0-7-5-1	8.9×10^{-9}
S. typhosa	1	—	10^{-3}	—	2.5×10^{8}	15.3	1-0-0-0-0-0-5-83-1-63	1.5×10^{-8}
	2	$0:1.6\times10^{7}$	10^{-3}	2.6×10^{8}	3.1×10^{8}	31.0	0-12-0-0-0-282-7-7-2-0	2.3×10^{-8}
Ps. aeruginosa	1	$1:7.2\times10^{5}$	10^{-4}	2.4×10^{8}	1.2×10^{7}	2.5	1-3-2-1-2-3-5-8-0-0	9.1×10^{-8}
	2	$1:8.8\times10^{5}$	10^{-4}	1.5×10^{8}	1.5×10^{7}	6.8	15-3-8-5-6-2-2-8-5-14	1.5×10^{-7}

TABLE VII

RELATION OF FREQUENCY OF STREPTOMYCIN RESISTANT MUTANTS AND SPEED OF LETHAL ACTION OF STREPTOMYCIN ON SENSITIVE CELLS

Species	Frequency of mutants resistant to concentrations of streptomycin μg./cc.			Speed of lethal action	
	25 μg./cc.	100 μg./cc.	1000 μg./cc.	10 μg./cc.	100 μg./cc.
H. influenzae	10^{-11}	10^{-11}	10^{-11}	2–6 hrs.	10 min.
H. pertussis	10^{-10} to $^{-11}$	10^{-10} to $^{-11}$	10^{-10} to $^{-11}$	4–24 hrs.	2 hrs.
E. coli	10^{-10}	10^{-10}	10^{-10}	6 hrs.	1 hr.
Shigellae	10^{-9} to $^{-10}$	10^{-9} to $^{-10}$	10^{-10}	4 hrs.	1–2 hrs.
Salmonellae	10^{-6} to $^{-7}$	10^{-9}	10^{-10} to $^{-11}$	0*	2–4 hrs.
S. typhosa	10^{-5} to $^{-6}$	10^{-8}	10^{-10} to $^{-11}$	0	4–24 hrs.
H. parapertussis	10^{-6}	10^{-8}	10^{-10} to $^{-11}$	0	>24 hrs.
Ps. aeruginosa	10^{-5} to $^{-6}$	10^{-7} to $^{-8}$	10^{-10}	0	4 hrs.

* Not primarily bactericidal.

It is of interest that with certain exceptions mutants resistant to streptomycin 1000 μg./cc. continue to exhibit this same degree of resistance when subcultured 20 times at 24 to 48 hour intervals in streptomycin-free medium.[1, 4, 5] From the results of study of the progeny of two colonies of each species, selected from those which formed in the presence of streptomycin 100 μg./cc., it is seen that some exhibit a decrease in resistance of a portion of the cells during 20 subcultures in the absence of streptomycin. However after the first subculture, which represents at least 10 generations, 100% of the popula-

TABLE VIII

DEGREE OF RESISTANCE EXHIBITED BY COLONIES FORMING IN MEDIA CONTAINING STREPTOMYCIN 25 AND 100 μg./cc.

Species	Isolated from μg./cc.	Total colonies isolated	Number of colonies which grew well on concentrations of streptomycin indicated—μg./cc.				
			0	25	100	1000	Strepto-mycin dependent
H. influenzae	25	28	26	28	20	17	2
	100	18	17		18	18	1
H. pertussis	25	41	41	41	41	39	0
	100	55	49		55	33*	6
E. coli	25	40	36	40	40	38	4
	100	48	32		48	47	16
Shigellae	25	44	36	44	43	37	7
	100	35	30		35	28	5
H. parapertussis	25	42	42	31	7	0	0
	100	91	91		86	0	0
Salmonellae	25	43	43	43	4	0	0
	100	53	52		53	1	1
S. typhosa	25	46	46	46	0†	0†	0
	100	47	47		47	0	0
Ps. aeruginosa	25	42	42	42	4	0	0
	100	47	47		47	0	0

* Only 33 tested.
† Only 23 tested.

tions of the progeny of resistant colonies continued to resist 100 μg./cc., save for the typhoid cultures (subculture 1, Table IV); only approximately 50% of these populations continued to show the same degree of resistance. The mutants of H. influenzae, H. pertussis, Shigella and E. coli strains which formed colonies in 25 or 100 μg./cc. appear not to change in resistance after 20 subcultures if one excludes streptomycin-dependent members. It is important to emphasize that most of these colonies represent mutants with a high degree of resistance.

In Salmonella, S. typhosa and Ps. aeruginosa, cultures of two colonies of mutants growing in 25 μg./cc. show a decrease in the fraction of their populations which continue to resist these concentrations of streptomycin during 20 subcultures in the absence of the antibiotic. However, in no instance was there evidence of change in degree of resistance during the first subculture, which represents at least 10 generations. Therefore these data offer evidence for inheritance of resistance to 25 and 100 μg./cc. In the four species showing a higher frequency of cells resistant to 25 and 100 μg./cc. most of the cells which form colonies in 25 μg./cc are sensitive to streptomycin 100 and 1000 μg./cc. They also appear to differ from the mutants resistant to 1000 μg./cc. in the stability of their resistance in the absence of streptomycin. The mechanism responsible is unknown; either mutation toward greater sensitivity or selection of a minute number of more sensitive cells by an environment which is more favorable for them than the resistant ones is possible.

Summary

Cells with varying degrees of resistance to streptomycin, 25, 100 and 1000 μg./cc., have been demonstrated in large populations of eight species of gram negative bacilli prior to exposure to streptomycin. These resistant variants exhibit traits characteristic of bacterial mutants and therefore arise spontaneously, independent of the action of streptomycin.

The known differences in therapeutic efficacy of streptomycin among infections caused by these eight species have been demonstrated to be closely correlated with two factors.

1. In infections in which streptomycin has been proven of therapeutic value—H. influenzae, H. pertussis and E. coli—the rate of occurrence of new mutants resistant to 25 and 100 μg./cc. is so low that they cannot be expected to play a significant role in emergence of resistance during streptomycin therapy.

In cultures of organisms causing infections in which streptomycin has been unsuccessful therapeutically—Salmonella, S. typhosa and Ps. aeruginosa—the rate of occurrence of mutants resistant to 25 and 100 μg./cc. is relatively high; these mutants doubtless play an important role in emergence of resistance to streptomycin and therapeutic failure.

2. Streptomycin in a concentration of 10 μg./cc. is primarily bactericidal against the species which cause infections in which streptomycin therapy has been of value. This concentration is not primarily bactericidal against those organisms causing infections in which streptomycin has failed therapeutically.

These data suggest that knowledge of these two factors in vitro can offer a reliable basis for predicting the therapeutic efficacy of streptomycin in a given infection. For example, in Shigella and H. parapertussis infections, in which streptomycin has not been clinically evaluated, one can predict success in the former and failure in the latter.

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SPANISH ABSTRACT

Base de Experimentación para Pronosticar la Eficacia Terapeutica de la Estreptomicina en Infecciones Causadas por Baccilos Negativos "Gram"

Las células con grados variables de resistencia a la estreptomicina, 25, 100 y 1000 μg./cc. han sido demostradas en grandes poblaciones de 8 especies de baccilos negativos "gram" antes de exponerse a la estreptomicina. Estos resistentes variantes exhiben características de mutantes bactéricos y por consiguiente aparecen espontaneamente, independientes de la acción de la estreptomicina.

Se ha demostrado que las diferencias conocidas en la eficacia terapeutica de la estreptomicina entre las infecciones causadas por estas 8 especies están muy correlacionadas con 2 factores:

1.—En infecciones en las cuales la estreptomicina ha sido de gran valor terapeutica—H. Influenca, H. pertussis y E. coli—la proporción de ocurrencia de nuevos mutantes resistentes a 25 μg./cc. es tan baja que no se puede esperar que tenga un papel importante en emergencia de resistencia durante la terapia de estreptomicina.

En cultivos de organismos que causan infecciones en las cuales la estreptomicina no ha tenido éxito terapeuticamente—Salmonela, S. tifosa y Ps. aeruginosa—la proporción de ocurrencia de mutantes resistentes a 25 y 100 μg./cc. es relativamente alta, estos mutantes indudablemente tienen un papel importante en emergencia de resistencia a la estreptomicina y fracaso terapeutico.

2.—La estreptomicina en una concentración de 10 μg./cc. es en primer lugar bactericida contra las especies que causan infecciones y cuya terapia de estreptomicina ha sido de valor. Esta concentración no es principalmente bactericida contra aquellos organismos que causan infecciones en las cuales la estreptomicina ha fracasado terapeuticamente.

Estos datos sugieren que el conocimiento de estos factores en vitro puedn ofrecer una base segura para pronosticar la eficacia terapeutica de la estreptomicina en cierta infección. Por ejemplo, en Shigella e infecciones H. parapertussis, en las cuales la estreptomicina no ha sido clinicamente avaluada, uno puede pronosticar éxito en la primera y fracaso en la segunda.

622 West 168th Street

CRANIO-FACIAL DYSOSTOSIS OF CROUZON

Report of a Case in Which the Malformation Occurred in Four Generations

By JAMES H. FLIPPEN, JR., M.D.
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CROUZON, in 1912, first described an hereditary malformation of the bones of the skull and face,[1, 2] occurring in a 29 year old woman and her 2½ year old son. It consisted of a hard protrusion in the region of the anterior fontanelle with widening of the transverse diameter of the skull and antero-posterior shortening. Other characteristics included beaked nose; relative prognathism due to hypoplasia of the maxilla; narrow, highly arched palate, and marked exophthalmos with divergent strabismus. Later, Crouzon[2] described a family in which seven of 21 members of two generations were affected. Roentgenologic examination[3] of these individuals revealed premature closure of various cranial sutures, greatly increased convolutional markings of the cranium and anterio-posterior flattening of the orbits. The skull bones were markedly thinned, especially over the protuberance at the bregma. Various deformities of the sphenoid and other bones of the base of the skull were also observed.[3]

Other examples of this deformity have been reported, largely from Europe, since the original descriptions. It is differentiated from other types of premature cranial synostosis by brachycephaly with a peak at the vertex in the region of the anterior fontanelle, a variation apparently dependent on the order in which the sutures close, and by a typical facies with beaked nose and prognathism due to deformities at the base of the skull, including hypoplasia of the superior maxilla. Exophthalmos is marked. Optic atrophy and divergent strabismus are common complications, as in other types of cranio-synostosis. Mental deficiency, probably due to the greatly increased intracranial pressure, is frequent.

Atkinson, in an extensive review[4] in 1937, counted 86 cases in which he believed the characteristics of the disease were unmistakable. However, only 58 of these fulfilled one of Crouzon's original criteria, that of heredity. Since then most of the reported cases have been of the so-called sporadic type. A notable exception was the report by Fogh-Andersen,[5] of a woman who had five children by two husbands. By the first she had one normal daughter and one with cranio-facial dysostosis. She bore the second husband a son with the malady and two dizygotic twins, one of whom was affected. Fogh-Andersen concludes that "the cranio-facial dysostosis of Crouzon may appear as a dominant hereditary affection, most likely a dominant mutation." The pedigree of the family to be reported in this paper apparently supports this hypothesis and is the first to be described in the English literature displaying the hereditary nature of the disease.

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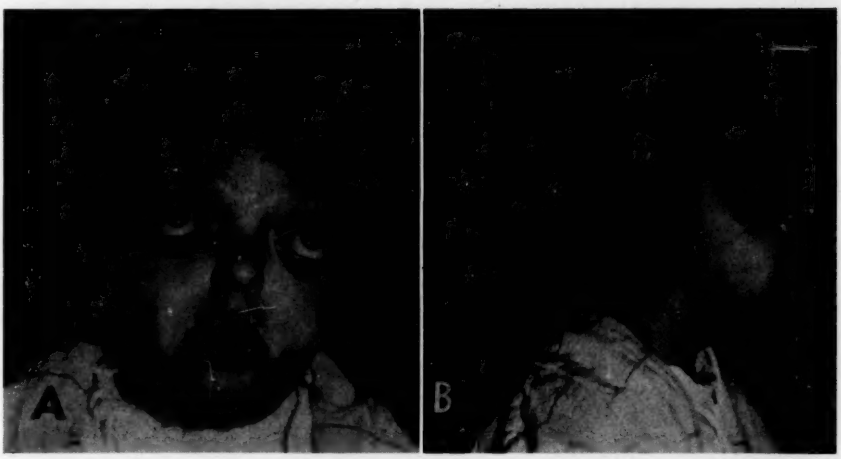


FIGS. 1A and B. Front and lateral views of G. S., showing extreme exophthalmos, divergent strabismus tendency to beaked nose and prognathism of lower jaw. Tongue is characteristically protruded.

CASE REPORT

G. S., a 4½ yr. old white American girl, entered Stanford University Hospitals with a complaint of bulging eyes since infancy and gradual impairment of vision.

Exophthalmos and cranial deformity, first noted at 1 mo. of age, had become progressively more marked (Fig. 1). About 5 mos. before entry she began running into objects she would previously have avoided and had to grope for familiar objects.

She was born at home after an 18 hr. labor and normal delivery. Birth wt. was 2.4 kg. She cried promptly after birth and was not cyanotic. Mother's pregnancy was complicated by episodes of uterine bleeding at 6 and 7 mos., for which she was kept in bed. Child's development was normal: she walked at 10 mos. and talked at 1 yr. of age. Occasional upper respiratory infections and otitis media were her only illnesses.

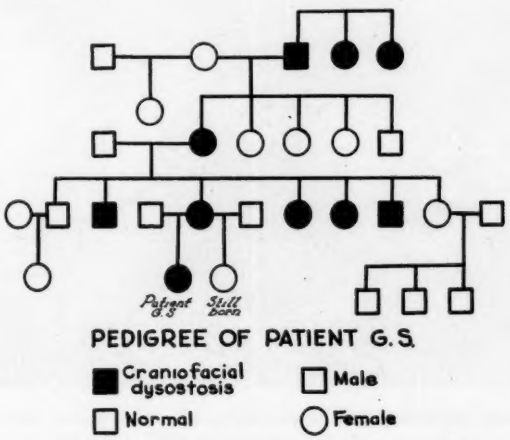
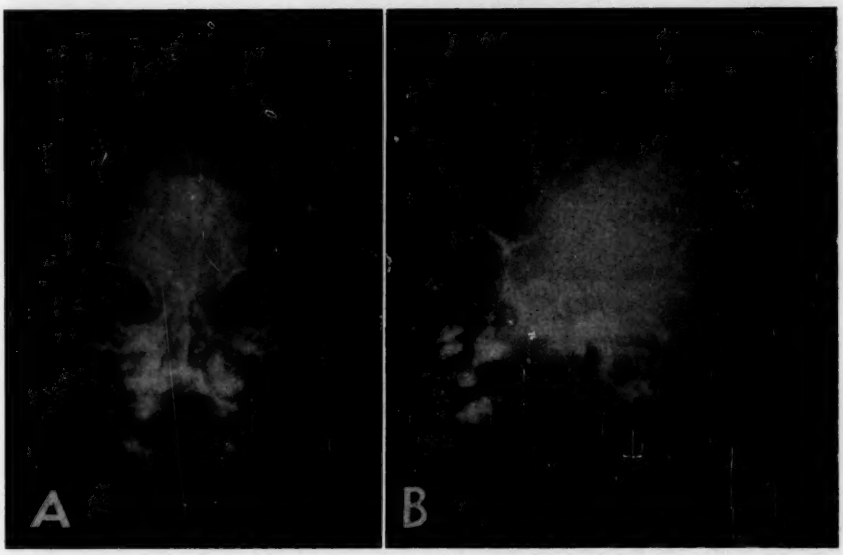


FIG. 2.

FIG. 3. Patient's maternal grandparents, maternal aunt who is blind, and maternal uncle.

FIGS. 4A and B. Front and lateral views of patient's mother. Note typical exophthalmos, divergent strabismus beaked nose and prognathism of mandible.

Family history is remarkable in that cranial deformity associated with exophthalmos and complicated by blindness is known to have been present in 4 generations of maternal ancestors (Fig. 2). Patient's great grandfather and 2 of his sisters were afflicted, as was 1 of his 5 children, the patient's maternal grandmother (Fig. 3). Patient's mother (Fig. 4) is affected and also 4 of the mother's 6 siblings, 2 male and 2 female. Of these 1 died at 9 mos. of age and another at 3½ yrs. The remaining 2 are almost totally blind. Patient's mother is the most mildly afflicted but has marked exophthalmos and divergent strabismus and recently has complained of failing eyesight. She has the typical peaked head, beaked nose and prognathism. Mother's normal brother and sister both have normal children.



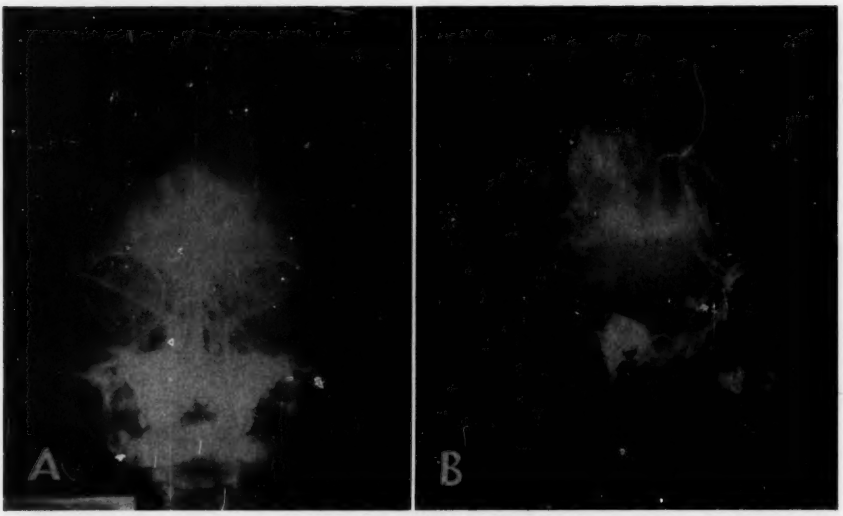
FIGS. 5A and B. Skull films of G. S., showing prominent convolutional markings, closed sutures, and bony protuberance in region of anterior fontanelle. Lateral view shows brachycephalic shape and prognathism of lower jaw.

Patient's mother had a stillbirth by her first husband who is said to have been luetic. A spontaneous abortion at 6 wks. terminated her only other pregnancy, which was by the patient's father. Patient's father is normal in appearance and has rather pleasant, regular features. He is employed as a farm laborer.

Physical examination showed a fairly well developed and well nourished white girl. Head was shortened antero-posteriorly with a bony protuberance in the region of the anterior fontanelle. Prognathism, apparently due to shortening of the maxilla, and beaked nose with a flat bridge were present. Exophthalmos was marked but the lids could cover the eyes. Divergent strabismus of 15 to 20 degrees, together with the prominent eyes and beaked nose, gave the child a bird-like appearance. She could not converge or fix an object with both eyes and there was wandering, rotary nystagmus. Pupils were equal, regular and reacted to light and accommodation. Retinae and retinal vessels were normal, but the discs were dead white and vision in both eyes was only 5/200. Protrusion of the lower jaw and tongue and underbite were present. Palate was highly arched. Speech was thick and lisping.

Heart and lungs were normal. Liver was palpable 2 cm. below the right costal margin. Genitalia and extremities were not remarkable. Reflexes were physiologic.

On entry, the temperature was 37° C., pulse 80, respirations 20, blood pressure 100/70. Stanford-Binet test, incomplete because of the visual defect, resulted in an I.Q. estimated to be between 65 and



FIGS. 6A and B. Skull films of G. S., 4 mos. after operation showing continued wide separation of craniectomies. Raised central portion is completely separated from remainder of skull.

80. Blood count and urine were normal. Wassermann reaction was negative. Nasopharyngeal and vaginal cultures grew the usual flora. Roentgen examination of the skull showed premature synostosis of all sutures except the spheno-occipitals. The basilar angle was acute and the orbits shallow. Deep convolutional markings indicated an increase of intracranial pressure of long standing (Fig. 5).

Patient developed a bilateral purulent otitis media a few days after entering the hospital which cleared promptly after myringotomies and treatment with penicillin. A modified Faber-Towne[6, 7] operation was done 1 mo. after admission to relieve the intracranial pressure and save the child's remaining vision. Two strips of bone about 1 cm. wide were removed on each side and parallel to the saggital suture. Transverse strips of bone, connecting these longitudinal excisions and carried

FIG. 7.

about 3 cm. lateral to them, were then removed over the coronal and lambdoid sutures. Polyethylene film was then wrapped over 1 edge of the longitudinal and transverse bone slits to prevent bony fusion, as suggested by Ingraham and his associates.[8] She withstood the operation well, made an uneventful recovery and was dismissed to her home 10 days later.

At the next visit 3 mos. later, her parents reported that they were greatly pleased with her improvement in vision and general well-being. Examination revealed an increase of visual acuity from the 5/200 in both eyes before operation to 15/200 on the right and 10/200 on the left. This was especially gratifying in view of the fact that optic atrophy is usually of a steadily progressive nature in this disease. Continued separation of the craniectomy borders by a distance of 0.5 to 1.0 cm. was shown by roentgenogram, despite some new bone growth (Fig. 6). When superimposed, the roentgenograms taken before and after surgery revealed considerable expansion in the outline of the skull (Fig. 7).

Discussion

Premature closure of cranial sutures has been explained by Park and Powers[9] as due to a genetic defect in the anlagen of the sutures. This seems much more satisfactory than other hypotheses, such as a mesodermal defect involving the bones at the base of the skull.[10] The latter does not plausibly account for abnormalities in shape of the calvarium because these are directly contingent upon the timing of closure of the various sutures. In the disease under discussion, the defect emerges as clearly hereditary and includes the calvarium as well as the base of the skull.

The fact that many cases of this type of premature closure occur sporadically,[4,11-15] indicates that the postulated chromosomal defect is a mutation or a recessive characteristic. The pedigree of the family reported above, as well as those of Crouzon[1,2] and Fogh-Andersen,[5] is compatible with either dominant or recessive genetic factors. If it is a recessive characteristic, the affected individuals, in order to have children with the disease, must be homozygous and mated to normal individuals who are heterozygous for the defect. It seems highly unlikely that such a rare defect would be present as a recessive factor in so high a proportion of the normal individuals accidentally mated to the members of the family exhibiting the deformity. Of the 44 individuals in the four sibships described above, 23 exhibited the characteristic deformities; therefore, if the characteristic is dominant, the afflicted persons can be assumed to be heterozygous, since the number of their children with the disease is about one half the total progeny.* Additional case histories are to be found in the literature.[15-24] There has been no report of a union between two persons with cranio-facial dysostosis. The small number of hereditary cases reported is readily understandable, since the severe facial deformity and disabling complications of the disease must greatly decrease the opportunities for marriage. So deleterious a genetic defect therefore tends to be eliminated by selection.

Summary

A case of cranio-facial dysostosis of Crouzon occurring in a 4 year old girl is described. The family tree of this patient is of particular interest because the deformity is known to have been present in 10 members of four generations, thus demonstrating the hereditary nature of the malformation. Because 10 of the 21 progeny were afflicted, the pedigree

* Dr. C. B. Danforth, Professor of Anatomy at Stanford University School of Medicine, who reviewed the data in this report, makes the following comments on the hereditary aspects: ". . . it would seem to me that the presumption is very strong that we are dealing with an hereditary trait. If so, it is clearly a dominant one since, if it were recessive, the general incidence of heterozygous individuals in the population according to my rough computation would be less than one in 160, and the chances of an affected father, daughter and granddaughter each marrying a heterozygous spouse would be not much greater than one in four million."

is interpreted as meaning that the disorder is the expression of an heterozygous, dominant trait. The patient was considerably benefited by the operation advocated by Faber and Towne for premature cranial synostosis, as modified by Ingraham.

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Spanish Abstract

Disostosis Cranio-Facial de Crouzon; Relato de un Caso en el Cual la Malformación Ocurrió en Cuatro Generaciones

Se describe un caso de disostosis cranio-facil de Crouzon que ocurrió en una niñita de cuatro años. El árbol genealógico de esta paciente es de particular interés a causa de la deformidad se sabe ocurrió en 10 miembros de cuatro generaciones, demostrado así la naturaleza hereditaria de la malformación En vista de que 10 de la prole fueron afectados, sè interpreta la genealogía de que el desorden es la expresión de una característica heterozigosa dominante. La paciente sacó gran beneficio de la operación recomendada por Faber y Towne para sinotosis cranial prematura, modificada por Ingraham.

Clay and Webster Streets

PENICILLIN REGIMENS IN PEDIATRIC PRACTICE

Study of Blood Levels

By GAVIN HILDICK-SMITH, M.D., THOMAS F. MCNAIR SCOTT, M.D., AND COLEMAN M. WHITLOCK, M.D.
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THE WIDE effectiveness of penicillin against a variety of commonly encountered pathogens and its lack of toxicity have led to a rather empiric method of dosage. In the early days when penicillin was scarce, attempts were made to use the minimum amount that would control any given infection. Now that penicillin is plentiful and relatively inexpensive, economy need not be the only consideration in working out a dosage schedule, but such things as the patient's comfort and the nursing time involved in giving injections become of greater importance. Furthermore, it is now justifiable for efforts to be made at reaching the dose, whether small or large, that is optimum for the infection under treatment.

The majority of commonly treated infections respond to minimal doses or, on the other hand, large doses are given unnecessarily. It seemed useful, therefore, to investigate a number of different dosage regimens in relation to the blood levels and the rates of plasma clearance produced. These observations might then act as a guide in applying penicillin therapy to a patient infected by an organism, the sensitivity of which was known or could be determined.

The action of penicillin *in vivo* probably cannot immediately be interpreted in terms of its action *in vitro,* yet as Eagle and Musselman[1] point out, "it is a reasonable surmise that the concentration of penicillin which is most rapidly effective against a given organism *in vitro* may also be the most effective *in vivo*." It is known that penicillin is rapidly bactericidal and not merely bacteriostatic, and that this bactericidal action depends on two factors which vary from organism to organism, and even from strain to strain in any given organism. These factors are: (1) the concentration of penicillin; (2) the time over which it is in contact with the organism in bactericidal concentration. By and large, the effective destruction of 99.9% of organisms depends on a product of these two factors; that is to say, a high concentration of drug acting over a short time will achieve the same result as a smaller concentration acting over a longer time. However, Eagle and Musselman[1] have demonstrated *in vitro* a curious zone phenomenon in certain strains of B hemolytic streptococci and staphylococci and occasionally in pneumococci, whereby a concentration higher than a certain optimum level prolongs the time necessary for effective killing.

A consideration of the optimal bactericidal level of penicillin and the time required for it to operate has been published by Eagle[2] for a number of organisms. He pointed

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This study was made under a contract with the Biological Division, Chemical Corps, Camp Detrick, Frederick, Md.

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out that 99.9% of the strains of streptococcus, staphylococcus and pneumococcus tested were killed in a range of penicillin concentration from 0.1 to 0.425 units/cc., and that the required time varied from 1½ hours for the streptococcus up to 20 hours for certain strains of the staphylococcus. If the original supposition is correct, the maintenance of concentrations in the body of the order and for the length of time indicated should overcome infections with organisms of the same degree of sensitivity.

The intramuscular injection of penicillin has been and probably still is the most commonly used method of giving penicillin. Initially, for sake of economy, small doses at three-hourly intervals were usually employed.

However, in 1946, Jawetz[3] showed that six or eight hour administration of the drug satisfactorily arrested hemolytic streptococcal infection in mice and, more recently, Zubrod[4] showed that 12- or 24-hourly intervals were as satisfactory as shorter intervals in protecting mice from the same infection, provided the total daily dose was the same. These experimental considerations led Marshall[5] to suggest that administration of penicillin at less frequent intervals could be used clinically with advantage. Tillett[6] had already shown that adults with pneumonia treated during the day with three hour doses, but not treated during the night, recovered satisfactorily; Schwentker[7] treated children with ordinary infections satisfactorily with doses of 10,000 u./lb. body weight/day in three doses, at eight-hourly intervals. György[8] and his colleagues successfully treated 40 children with various infections with two doses of crystalline penicillin in 24 hours, children under three years receiving 50,000 u. per dose and older children, 100,000 u.

In the evaluation of these different dosage schemes, it became clear that there were periods, which might extend for some hours, during which the patient had no detectable circulating penicillin. Zubrod[4] particularly emphasized this in his mouse experiments, and the importance of penicillin blood levels began to be called in question.[5] However, it is possible to adopt the point of view that because of the damage to the organisms caused by the high blood levels resultant upon the large doses given, the necessity for continuous bactericidal levels is lessened. Support is lent to this viewpoint by the work of Parker and his colleagues,[9, 10] who showed that, following a short exposure of organisms to an adequate concentration of penicillin *in vitro,* a period of bacteriostasis occurs which, in the case of Staph. aureus, is approximately three hours. At the end of this time, regeneration and multiplication occurs again, and it is during this logarithmic phase that the organism is most susceptible to penicillin. Another explanation for the lessened need for a continuous plasma level may be found in the work of Shacter[11] who reported a longer duration of bactericidal levels of penicillin in the lymph than in the plasma.

The findings to be described appear to indicate that there is a common denominator to all these various successful penicillin dosage schemes; namely, the maintenance of bactericidal levels in the blood and/or tissues for an adequate length of time. The dose must be large enough to produce optimal bactericidal levels and must be frequent enough to prevent much regeneration of the infecting organisms, but within these two limits any number of combinations can be effective, and the one chosen may depend on such factors as convenience for those administering the drug and the comfort of the patient.

In clinical practice, a large number of children suffer from easily controlled infections with sensitive organisms, so that almost any reasonable regimen of penicillin therapy may be effective. However, when the patient does not respond as expected, a critical review of the type of therapy being employed is called for. Under such circumstances, the following

questions relating to the use of penicillin may be asked:

1. Is the child infected with an organism that is less sensitive to penicillin action than usual? An accurate measurement of penicillin sensitivity should then be made.

2. Is the dose of penicillin too small and/or the interval between doses too long to maintain a bactericidal level for the necessary length of time to destroy a high percentage of the infecting organisms? This question can be answered by the answer to question 1, together with an accurate estimation of blood levels in the patient.

3. Is the infection so great that, although 99.9% of the organisms are destroyed in a given length of time, the actual number not destroyed is maintaining the infection? In this case, the answers to questions 1 and 2 may indicate that the organism is sensitive to the levels produced in the patient's blood with the dose given, and that the time interval at which that level is maintained is one commonly known to be effective. Raising the dose and prolonging the time of bactericidal plasma level by decreasing the interval between doses may achieve the required results by killing an even higher percentage of the organisms and thus reducing the absolute number present.

4. Is the site of the infection such that the organisms are protected from the full action of penicillin by being in the pus of abscesses, in the purulent exudate of serous cavities, or in vegetations on a heart valve? In such a case, high blood levels may be needed in order to provide a sufficient "head of pressure,"[12] so that bactericidal amounts of penicillin may diffuse through the protective covering to reach the organisms.

5. Can the reason for failure of therapy be the "zone phenomenon" described above? This is a new observation and it is not certain that such a phenomenon occurs *in vivo,* yet one might consider its occurrence if there was failure to respond in the face of high blood levels, a sensitive organism and no evidence of abscess formation.

In order to adjust penicillin therapy to the individual patient, a knowledge of the different forms of commercially available penicillin and routes of administration and how they act in relation to plasma penicillin levels is necessary. In this study, an arbitrary choice of certain regimens was made; the results obtained must not be construed as mutually exclusive of other regimens, but merely as illustrating a general principle of therapy. The regimens studied were:

A. Intramuscular injection of aqueous penicillin at various dosages and at various time intervals.

B. The addition of orally administered "staticin" caronamide to the above.

C. Intramuscular injection of aqueous procaine penicillin.

D. The addition of orally administered "staticin" caronamide to the above.

E. Orally administered penicillin, both buffered and unbuffered, with and without "staticin" caronamide.

Materials and Methods

Afebrile convalescent children between the ages of 2 to 11½ yrs., with normal renal functions, were used for the study.

All the penicillin used was crystalline penicillin G.*

Part of the aqueous procaine penicillin† used consisted of material in which 75% of particles were 75 to 100 microns in diameter = procaine penicillin A, and part of a preparation‡ in which

* Crystalline penicillin G was supplied by Commercial Solvents Company and is their standard commercial product.

† Procaine penicillin A was that produced and supplied by Wyeth, Inc.

‡ Procaine penicillin B was that produced commercially by E. R. Squibb & Sons, Inc.

TABLE I

INTRAMUSCULAR AQUEOUS PENICILLIN IN A SINGLE DOSE OF APPROXIMATELY 500 U./LB.

No. of Tests			Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	1½
	Mean		533	1.08	0.24
	Median		500	1.18	0.2
10		High	685	1.9	0.36
	Range				
		Low	470	0.48	0.08

95% of the particles were less than 50 microns with a range of 5 to 150 microns = procaine penicillin B.

Caronamide* was used either in the form of crushed tablets of "staticin" caronamide or of the liquid preparation of cremostaticin®, which contains 20% caronamide in suspension.

Penicillin blood levels were measured by 1 or 2 microbiologic technics.

At the beginning of the study, a modified Rammelkamp[13] method was used. This had the disadvantage of requiring relatively large amounts of blood. Later, a micromethod of bio-assay was developed,[14] based on the principles described by Fielding.[15] Sufficient blood for this could be

TABLE II

INTRAMUSCULAR AQUEOUS PENICILLIN IN A SINGLE DOSE OF APPROXIMATELY 5000 U./LB.

No. of Tests			Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	1	3	5
	Mean		5304	16.37	6.72	0.35	0.037
	Median		5086	15.8	6.13	0.27	0.023
24		High	6666	26.8	12.1	1.62	0.14
	Range						
		Low	4545	9.25	2.26	0.09	0

obtained from a finger prick. Several comparisons of the 2 methods on material containing known amounts of penicillin revealed that the micromethod was able to detect these amounts of penicillin almost quantitatively, whereas the Rammelkamp method consistently detected less by a factor of 1.6.[14] In the final tabulation of results, the figures obtained by the 1st method have been multiplied by this factor to make them comparable.

The injections of penicillin were measured and given by one of the authors and the blood obtained for testing by the appropriate means and at the appropriate times after injection.

RESULTS

A. Intramuscular Aqueous Penicillin: Tables I and II compare the plasma penicillin clearances obtained after the single administration of varying intramuscular doses of aqueous penicillin. The effect of the common practice of giving small doses, 4 to 5000 u./lb./24 hrs. at 3-hourly intervals is illustrated by the blood level curve obtained after a single dose of 500 u./lb. (Table I). This dose maintains, on an average, a level of over 0.1 u. for 2 hrs. The more recent trend towards giving larger doses at less frequent intervals is illustrated by the curve following a single dose of 5000 u./lb., where the same level was obtained for 4 hrs. (Table II).

* The caronamide and cremostaticin® was supplied by Sharp & Dohme, Inc. Cremostaticin® is a 20% suspension of caronamide in a sweetened medium.

TABLE III

INTRAMUSCULAR AQUEOUS PENICILLIN IN A SINGLE DOSE OF APPROXIMATELY 5000 U./lb.; CARONAMIDE IN INDIVIDUAL DOSES OF 0.036 TO 0.055 GM./LB. GIVEN ORALLY EVERY 4 HRS.

No. of Tests			Dosage in U./lb.	Serum Penicillin Levels in U./cc at Hrs. After Dose				
				½	1	3	5	7
	Mean		5454	26.6	15.4	2.48	0.58	0.1
	Median		5486	26.3	13.3	2.24	1.14	0.02
15	Range	High	6666	37.0	26.0	6.67	1.7	0.47
		Low	4779	8.9	6.75	0.53	0.09	0

In light of these findings, it is interesting to refer briefly to the clinical results in 92 children treated for bacterial pneumonia with penicillin alone at The Children's Hospital of Philadelphia during the last 2 yrs.[16] The total daily dose varied from 5000 u./lb. to 20,000 u./lb. and the intervals of administration from every 3 hrs. to every 12 hrs. The clinical response appeared to be equally good whether the interval was 3-hourly or 12-hourly, provided a minimum of 5000 u./lb. were given in 24 hrs. when 3-hourly doses were given, and a minimum of 10,000 u./lb. in 24 hrs., with the longer dosage intervals.

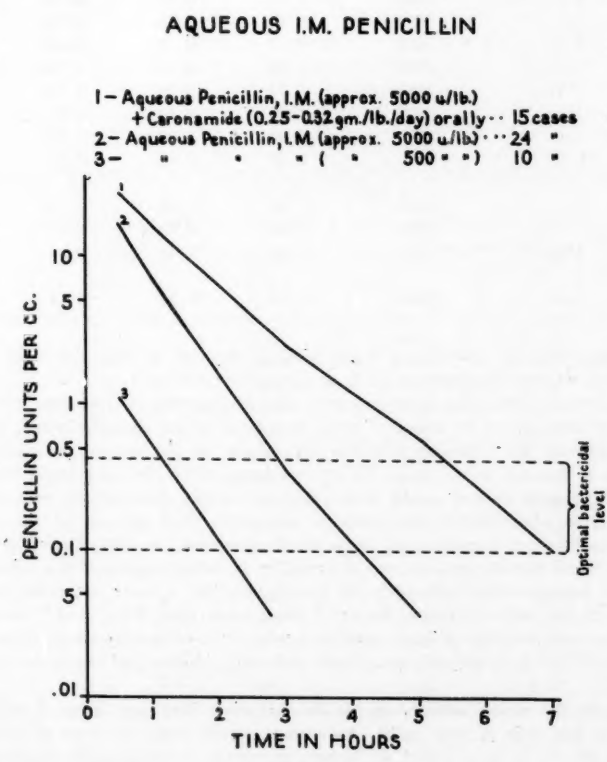
AQUEOUS I.M. PENICILLIN
1 – Aqueous Penicillin, I.M. (approx. 5000 u/lb.)
+ Caronamide (0.25–0.32 gm./lb./day) orally · · 15 cases
2 – Aqueous Penicillin, I.M. (approx. 5000 u/lb.) · · · 24 "
3 – " " " (" 500 " ") 10 "
PENICILLIN UNITS PER C.C.
10
5
1
0.5
0.1
5
.01
Optimal bactericidal level
0 1 2 3 4 5 6 7
TIME IN HOURS

CHART 1

B. Intramuscular Aqueous Penicillin with Oral Caronamide: The recent discovery that "staticin" caronamide (4 carboxy phenyl methane sulfonanilide) blocks the tubular excretion of penicillin[17] and thus delays the clearance from the blood has introduced a new variable into the management of penicillin therapy.[18, 19] This drug was given to 15 children in doses of 0.25 to 0.32 mg./lb./24 hrs. This dosage range has been shown to be adequate for complete suppression of tubular excretion of penicillin in the average child.[20] Aliquots of the total 24 hr. dose were given every 4 hrs., starting 4 hrs. before the single intramuscular dose of penicillin and continuing for 12 hrs. following it. Under this regimen, high initial serum levels were obtained and bactericidal levels were still present at 7 hrs. (Table III). Because of the opinion of Eagle et al.[1] that levels of penicillin over the maximum of the optimum range represent so much wasted drug or may actually be detrimental because of the zone phenomenon in certain organisms, it is probably wise not to use this regimen routinely, but to reserve it for the treatment of infections with organisms of higher resistance. In this case, the upper limit of

TABLE IV

PROCAINE PENICILLIN A IN A SINGLE INTRAMUSCULAR DOSE OF APPROXIMATELY 3000 U./LB.

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	3	24	48
1	B.C.	2770	0.72	0.36	0.12	0
2	B.L.	2770	1.40	1.40	0	0
3	A.G.	3480	2.90	0.96	0.18	0
4	A.G.	3480	0.96	0.48	0.12	0.18
5	K.F.	3000	0.72	0.96	0.30	0
6	K.F.	3000	1.40	0.72	0.24	0.18
7	T.W.	2666	0.72	0.96	0.18	0
8	E.G.	3570	1.40	1.40	0.09	0.18
9	A.F.	3000	1.90	1.90	0.18	0
10	L.D.	3000	1.90	0.96	0.12	0
Mean		3073	1.40	1.01	0.15	
Median		3000	1.40	0.96	0.15	
Range	High	3570	2.90	1.96	0.36	
	Low	2666	0.72	0.36	0	

the optimal range would be shifted to a higher level on the scale of penicillin units. The results of the observations recorded in sections A and B are summarized in Chart 1.

C. Aqueous Procaine Penicillin Intramuscularly: The development of a procaine salt of penicillin represents an extension of the search to find a method of giving penicillin which would lessen frequency of injections. By combining penicillin with peanut oil and beeswax, Romansky and Rittman[21] were able to prolong, up to 24 hrs., the interval during which detectable blood levels could be obtained. Although good clinical results were reported,[22] certain disadvantages were encountered, namely, difficulty in administration, variability of absorption, local pain at the site of injection, sensitivity to peanut oil or beeswax, and sterile abscess formation. In 1947, Herrell et al.[23] and in 1948 Sullivan[24] found that the procaine salt of penicillin G, when suspended in a refined vegetable oil and injected intramuscularly into adults in doses of 300,000 u., gave detectable plasma levels for as long as 24 hrs. and occasionally longer. A short while later, Price et al.[25] observed that a suspension of procaine penicillin in water regularly produced a prolongation, up to 24 hrs. or longer, of plasma penicillin levels in the majority of both adults and children, and was more consistent than the oil product.

Table IV gives the results obtained in 10 children when individual doses of 3000 u./lb. of aqueous procaine penicillin A were given. An average plasma penicillin level of 1.4 u./cc. was detectable at ½ hr.; 1.0 u./cc. at 3 hrs.; by 24 hrs., an average of 0.15 u./cc. was still detectable in 9 of the 10 patients, while at 48 hrs., 3 patients still showed levels averaging 0.18 u./cc.

TABLE V

PROCAINE PENICILLIN A IN A SINGLE INTRAMUSCULAR DOSE OF APPROXIMATELY 6000 U./LB.

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	3	24*	48	72
1	E.O.	7140	3.80	1.90	0.48	0.24	0.12
2	A.G.	6976	2.90	1.90	0.72	0	0
3	W.B.	6000	1.90	1.90	0.24	0.24	0.06
4	B.S.	5540	5.80	3.80	0	0	0.12
5	K.F.	6000	1.90	1.90	0.48	0.24	0.06
6	A.G.	5454	0.48	0.96	0.48	0.06	0
7	D.N.	6250	1.90	0.96	0.48	0	0.24
8	H.J.	6200	5.80	1.40	0.48	0.24	0.24
9	A.L.	6120	5.80	5.80	0.36	0.12	—
10	M.M.	6666	3.80	0.96	0.48	0	—
11	V.M.	6250	1.90	0.96	0.36	0	—
12	L.R.	6666	1.90	1.90	0.36	0	—
Mean		6272	3.15	2.03	0.41	0.10	
Median		6225	2.40	1.90	0.48	0.06	
Range	High	7140	5.80	5.80	0.72	0.24	
	Low	5454	0.48	0.96	0	0	

TABLE VI

PROCAINE PENICILLIN B IN A SINGLE INTRAMUSCULAR DOSE OF APPROXIMATELY 6000 U./LB.

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose* ½	3	24
1	B.S.	5684	0.48	0.36	0.12
2	B.S.	5684	1.92	1.92	0.09
3	E.O.	6000	0.36	0.48	0.48
4	E.O.	6000	3.84	0.96	0
5	P.S.	6000	0.72	0.48	0.06
6	P.S.	6000	3.84	0.96	0.06
7	W.B.	6000	1.44	0.72	0.12
8	W.B.	6000	0.96	0.48	0.24
9	H.W.	6000	2.88	1.92	0
10	H.W.	6000	1.92	1.92	0.06
Mean		5842	1.84	1.02	0.12
Median		6000	1.68	0.84	0.08
Range	High	6000	3.84	1.92	0.48
	Low	5842	0.36	0.36	0

* "O" is actually <0.06 u./cc.

TABLE VII

PROCAINE PENICILLIN A IN A SINGLE INTRAMUSCULAR DOSE OF 10,000 U./LB.

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc at Hrs. After Dose ½	3	48
1	B.S.	10,000	2.60	1.90	0.03
2	A.G.	10,000	1.90	1.90	0.06
3	C.B.	10,000	3.80	1.30	0.12
4	J.B.	10,000	1.90	1.90	0.24
5	G.C.	10,000	1.90	0.96	0.24
6	M.G.	10,000	5.80	3.80	0.12
7	J.H.	10,000	2.40	2.40	0
8	W.B.	10,000	0.72	1.40	0.12
9	B.S.	10,000	1.90	1.90	0.24
Mean		10,000	2.54	1.94	0.13
Median		10,000	1.90	1.90	0.12
Range	High	10,000	5.80	3.80	0.24
	Low	10,000	0.72	0.96	0

Each of another group of 12 patients received the same material in individual doses of 6000 u./lb. Table V): at ½ hr., the average level was 3.15 u./cc.; at 3 hrs., 2.0 u./cc.; at 24 hrs., 0.5 u./cc.; at 48 hrs., 0.16 u./cc.; at 72 hrs., 4 of 8 levels taken gave an average of 0.16 u./cc. One of the patients showed no level at 24 and 48 hrs., but had a level of 0.12 u./cc. at 72 hrs.

A parallel study was made of 15 trials in 6 patients, each of whom on each trial received approximately 6000 u./lb. of procaine penicillin B (Table VI); at ½ hr., the average level of the 15 trials was 1.35 u./cc.; at 3 hrs., 0.8 u./cc.; at 24 hrs., 0.1 u./cc. It would appear that this preparation (procaine penicillin B), with the smaller particle size, did not lead to such prolonged levels; however, it was much more easily handled, as far as the technicalities of injection were concerned.

Each of another 9 patients received an individual dose of approximately 10,000 u./lb. of procaine penicillin A (Table VII). The average level at ½ hr. was 2.5 u./cc.; at 3 hrs., 1.9 u./cc., and at 48 hrs., 0.13 u./cc., which showed little change from the smaller dose of 6000 u./lb.

From these results, it would seem that a single intramuscular dose of approximately 6000 to 10,000 u./lb. of aqueous procaine penicillin, which maintains the plasma penicillin at a theoretically optimal bactericidal level for a period longer than that required for the destruction of 99.9% of sensitive organisms *in vitro*,[1] might be expected to bring about good clinical results. This supposition

TABLE VIII

55 CHILDREN HOSPITALIZED FOR ACUTE RESPIRATORY INFECTIONS OF BACTERIAL ORIGIN. RESULTS OF TREATMENT WITH SINGLE DAILY DOSES OF APPROXIMATELY 6000 U./LB. OF PROCAINE PENICILLIN

Type of Infection	No. of Patients	No. of Therapeutic Failures
Pneumonia	13	0
Nasopharyngitis and/or Tonsillitis	18	0
Peritonsillar Abscess	1	0
Otitis Media	23	3*

* In 2 of these patients the infecting organisms were reported as insensitive to penicillin.

TABLE IX

PROCAINE PENICILLIN A IN A SINGLE INTRAMUSCULAR DOSE OF 10,000 U./LB.; CARONAMIDE IN INDIVIDUAL DOSES OF 0.045 GM./LB. GIVEN ORALLY EVERY 4 HRS.

No. of Test	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. ½	3	24
1	B.M.	10,000	2.40	2.40	1.90
2	R.P.	10,000	1.40	1.40	0.96
3	A.L.	10,000	2.40	2.40	1.90
4	E.O.	10,000	1.90	1.90	0.96
Mean		10,000	2.13	2.13	1.43
Median		10,000	2.15	2.15	1.43
Range	High	10,000	2.40	2.40	1.90
	Low	10,000	1.40	1.40	0.96

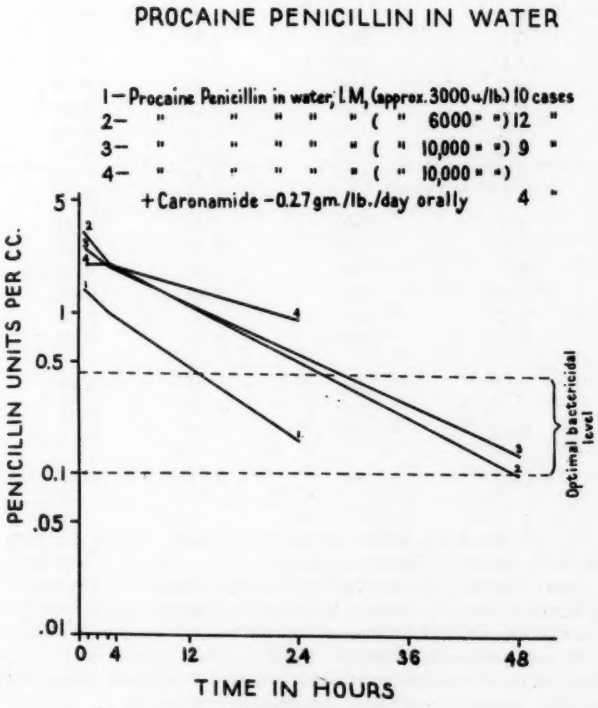
PROCAINE PENICILLIN IN WATER
1—Procaine Penicillin in water, I.M. (approx. 3000 u./lb.) 10 cases
2— " " " " " (" 6000 " ") 12 "
3— " " " " " (" 10,000 " ") 9 "
4— " " " " " (" 10,000 " ")
+Caronamide—0.27 gm./lb./day orally 4 "
PENICILLIN UNITS PER CC.
5
1
0.5
0.1
.05
.01
Optimal bactericidal level
0 4 12 24 36 48
TIME IN HOURS

CHART 2

is supported by the report of Boger,[26] who successfully treated pneumonia in adults by using single injections of the procaine penicillin in oil, and by our own observations at The Children's Hospital of Philadelphia. At this institution, a 3 mos.' trial was instituted whereby the routine method of using penicillin was to give 1 injection a day of 6000 u./lb. body weight of aqueous procaine penicillin. The material used was procaine penicillin B (see Table VI), because of the technically easier management of this product in comparison with procaine penicillin A. Of the 55 children treated, only 3 failed to respond (Table VIII).

D. Procaine Penicillin with Caronamide: It seemed important to discover whether the concomitant use of oral caronamide would raise and prolong the blood levels achieved by aqueous procaine penicillin alone. Each of a small group of 4 patients was given a single intramuscular injection of 10,000 u./lb. of procaine penicillin A, together with caronamide in a dosage of 0.25 to 0.30 gms./lb./

TABLE X

UNBUFFERED PENICILLIN IN A SINGLE ORAL DOSE OF APPROXIMATELY 3000 U./LB.

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	1½	3
1	R.A.	1860	1.04	0.26	0
2	C.O.	3210	1.04	0.26	0
3	G.F.	2680	0.52	0.78	0
4	R.A.	1560	0.64	0.32	0.12
5	G.F.	2680	0.48	0.96	0.24
6	A.J.	2200	0.48	0.32	0.32
7	A.G.	3440	1.28	0.64	0.64
8	B.S.	2780	0.12	0.06	0
9	S.H.	3150	0.64	0.24	0
10	W.R.	2500	0.24	0.12	0
11	R.J.	2400	0.48	0.12	0.12
12	P.S.	3110	0.16	0.08	0
13	T.J.	2400	0.48	0.24	0.18
14	E.B.	2680	0.48	0.24	0
15	J.S.	2500	0.24	0.16	0
16	G.E.	2350	0.48	0.08	0.08
17	E.O.	3555	0.96	0.72	0.36
18	A.G.	3080	0.18	0.12	0.09
Mean		2673	0.55	0.32	0.12
Median		2680	0.48	0.26	0.04
Range	High	3555	1.28	0.96	0.64
	Low	1560	0.12	0.06	0

24 hrs. orally, the total dose being divided into 4-hourly aliquots of 0.045 gm. (avg.). The results are tabulated in Table IX, the average levels being 2 u., 2 u. and 1.4 u., respectively, at ½, 3 and 24 hrs. These results indicated that the height of the initial blood level was limited by the rate of absorption and therefore was not influenced by caronamide, but that the decreased rate of excretion of the penicillin that was absorbed led to a slow rate of plasma clearance. By repeated daily use of procaine penicillin and caronamide, a high level might eventually be built up. However, if high levels are required, these are better achieved by crystalline penicillin as discussed earlier. Chart 2 summarizes graphically the results obtained in experiments described under C and D.

E. Oral Penicillin: This form of penicillin therapy is used extensively in practice. It may be a reliable method in early infancy,[27, 28] since absorption appears to be good, possibly due to the achlorhydria[29] frequently present at this age, but in older children and adults, absorption from the alimentary tract is variable. There is a difference of opinion as to the importance of antacids in

TABLE XI

BUFFERED PENICILLIN IN A SINGLE ORAL DOSE OF APPROXIMATELY 3000 U./LB.

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	1½	3	4½	6
1	J.S.	2500	0.24	0.24	0.24	0	0
2	P.S.	3110	0.24	0.18	0.24	0.06	0
3	A.G.	3080	0.32	1.30	0.08	0	0
4	K.F.	3000	0.24	1.90	0.24	0.18	0.18
5	H.J.	2750	0.96	0.36	0.24	0.18	0
6	W.B.	2000	0.48	0.36	0.18	0.12	0
7	E.O.	3550	0.72	0.48	0.18	0.12	0
8	C.O.	3210	1.92	0.96	0.32	0.24	0.24
9	S.H.	3425	0.48	0.18	0.18	0.06	0
10	B.S.	2780	0.24	0.24	0.12	0	0.06
Mean		2940	0.58	0.62	0.20	0.10	
Median		3040	0.40	0.36	0.21	0.09	
Range	High	3550	1.92	1.90	0.32	0.24	
	Low	2000	0.24	0.18	0.08	0	

TABLE XII

UNBUFFERED PENICILLIN IN A SINGLE ORAL DOSE OF APPROXIMATELY 3000 U./LB.; CARONAMIDE (TABLET FORM) IN A SINGLE DOSE OF 0.045 GM./LB. GIVEN ORALLY AT THE SAME TIME AS PENICILLIN

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	1½	3	4½	6
1	C.D.	3210	0.24	0.48	0.32	0.16	0.12
2	G.F.	2680	0.16	0.24	0.16	0.12	0
3	M.B.	2200	0.72	0.48	0.09	0	0
4	A.J.	2200	0.24	0.24	0.09	0	0
5	A.G.	3440	0.72	0.36	0.09	0.6	0
6	A.G.	3440	0.12	0.12	0.06	0	0
7	B.S.	2780	0.24	0.18	0.12	0	0
8	B.S.	2780	0.24	0.72	0.36	0.12	0.06
9	B.S.	2780	0.06	0.24	0.06	0	0
10	S.H.	3150	0.36	0.24	0.18	0.09	0
11	R.J.	2440	0.48	0.36	0.18	0	0
12	R.J.	2400	0.24	0.18	0.12	0	0
Mean		2791	0.32	0.32	0.15		
Median		2780	0.24	0.24	0.12		
Range	High	3440	0.72	0.72	0.36		
	Low	2200	0.06	0.12	0.06		

improving absorption, some authors stressing their importance,[20, 21] while others state that the part antacids play is insignificant.[22] There is a general feeling that the oral dose should be about 5 times[23] the intramuscular dose and given at 2- to 3-hourly intervals.

In this study, commercial penicillin G, unbuffered* or buffered,† was given 3 hrs. after breakfast, as a single dose of approximately 3000 u./lb. (equivalent to 24,000 u./day, or 5 times an average 3-hourly intramuscular dose).

1. Unbuffered penicillin given as above to 18 patients resulted in an average plasma penicillin level at ½ hr. of 0.5 u./cc., and at 1½ hrs. of 1.3 u./cc.; at 3 hrs., only half the cases showed a level which averaged 0.2 u./cc. (Table X).

TABLE XIII

UNBUFFERED PENICILLIN IN A SINGLE ORAL DOSE OF APPROXIMATELY 3000 U./LB. CARONAMIDE (CREMOSTATICIN FORM) IN A SINGLE DOSE OF 0.045 GM./LB. GIVEN ORALLY AT THE SAME TIME AS PENICILLIN

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	1½	3	4½	6
1	B.S.	2780	0.48	0.24	0.18	0.18	0.12
2	A.G.	3440	1.44	0.96	0.24	0.12	0
3	A.G.	3440	0.64	1.92	0.12	0.08	0.08
4	B.S.	2780	0.18	0.48	0.24	0.06	0
5	R.J.	2400	1.92	1.44	0.18	0.16	0
6	R.J.	2400	0.96	0.24	0.12	0	0
7	R.J.	2400	0.96	0.36	0.12	0	0
8	B.S.	2780	0.48	0.24	0.16	0.12	0
9	B.S.	2780	0.36	0.09	0.12	0.09	0
10	T.J.	2500	0.06	0.18	0.06	0.18	0
11	T.J.	2500	0.24	0.12	0.06	0	0
12	T.J.	2500	0.24	0.12	0.24	0.12	0.08
13	E.B.	2680	0.18	0.18	0.09	0	0
14	P.S.	3110	0.48	0.08	0.08	0.12	0.08
15	A.G.	3440	0.72	0.48	0.09	0	0
16	E.O.	3555	0.96	0.16	0.08	0.16	0
17	F.O.	3555	0.36	0.72	0.48	0.18	0.12
18	T.W.	2660	0.24	0.30	0.32	0.08	0
19	T.W.	2660	0.12	1.90	0.48	0.12	0
20	T.W.	2660	0.24	0.48	0.48	0.24	0.12
Mean		2802	0.56	0.58	0.19	0.10	
Median		2730	0.36	0.30	0.14	0.10	
Range	High	3555	1.92	1.92	0.48	0.24	
	Low	2400	0.06	0.08	0.06	0	

2. Buffered penicillin given in the same way to 10 patients led to a slightly better result. Average levels of 0.58 and 0.6 were obtained at ½ and 1½ hr. periods, respectively, while all 10 showed an average level of 0.2 u./cc. at 3 hrs., and 7 of the 10 an average level of 0.13 u./cc. at 4½ hrs. (Table XI).

3. Unbuffered penicillin given as above with single dose of caronamide (0.045 gm./lb.) to each of 12 patients gave average blood levels at ½, 1½ and 3 hrs. of 0.3, 0.3 and 0.15 u./cc., respectively,

* Unbuffered penicillin was supplied by Commercial Solvents Company and is their standard commercial product.

† The buffered penicillin used in this study is the commercial product of Eli Lilly & Company.

TABLE XIV

BUFFERED PENICILLIN IN A SINGLE ORAL DOSE OF APPROXIMATELY 3000 U./LB. CARONAMIDE (CREMOSTATICIN FORM) IN A SINGLE DOSE OF 0.045 GM./LB. GIVEN ORALLY AT THE SAME TIME AS PENICILLIN

No. of Tests	Patients Tested	Dosage in U./lb.	Serum Penicillin Levels in U./cc. at Hrs. After Dose ½	1½	3	4½	6
1	T.J.	2500	0.24	0.12	0.24	0.12	0.08
2	E.O.	3555	0.48	0.32	0.12	0.08	0
3	E.O.	3555	0.36	0.72	0.48	0.18	0.12
4	A.G.	3000	0.24	1.30	0.08	0.08	0
5	T.W.	2666	0.24	1.30	0.32	0.08	0
6	T.W.	2666	0.12	1.90	0.48	0.12	0
7	T.W.	2666	0.24	0.48	0.48	0.24	0.12
8	B.S.	2780	0.48	0.24	0.18	0.18	0.12
9	A.G.	3425	0.18	0.12	0.09	0	0
10	E.O.	3555	0.24	0.48	0.09	0.06	0
Mean		3037	0.282	0.698	0.26	0.114	
Median		2890	0.24	0.48	0.21	0.10	
Range	High	3555	0.48	1.90	0.48	0.18	
	Low	2500	0.12	0.12	0.09	0	

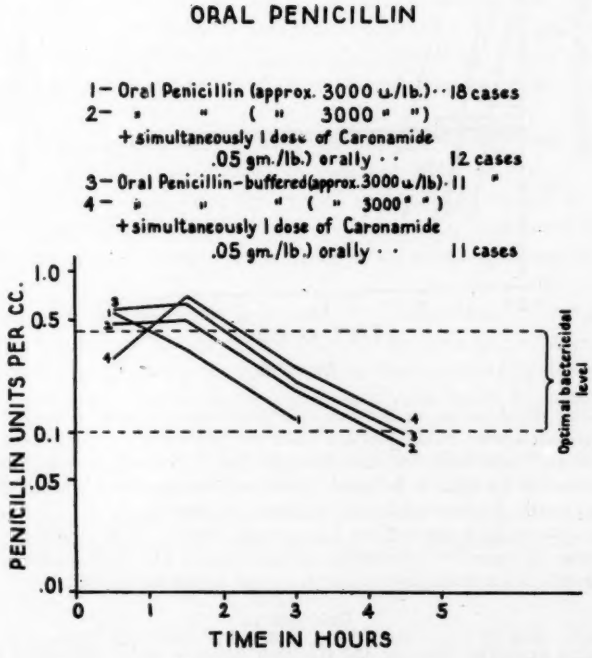
ORAL PENICILLIN
1 – Oral Penicillin (approx. 3000 u./lb.) · · 18 cases
2 – " " (" 3000 " ") + simultaneously 1 dose of Caronamide .05 gm./lb.) orally · · 12 cases
3 – Oral Penicillin-buffered (approx. 3000 u./lb) · 11 "
4 – " " " (" 3000 " ") + simultaneously 1 dose of Caronamide .05 gm./lb.) orally · · 11 cases
PENICILLIN UNITS PER CC.
1.0
0.5
0.1
.05
.01
0
1
2
3
4
5
TIME IN HOURS
Optimal bactericidal level

CHART 3

while 5 out of the 12 showed levels averaging 0.1 u./cc. at 4½ hrs. (Table XII). In a similar experiment, Table XIII, in which caronamide was administered as cremostaticin®, instead of caronamide tablets, to 20 patients, slightly better results were obtained. Average levels were 0.47, 0.48 and 0.18 u./cc. at ½, 1½ and 3 hrs., respectively, while 15 of the 20 patients showed an average level of 0.16 u./cc. at 4½ hrs. These findings suggest that caronamide in the form of cremostaticin® is a slightly better enhancing agent than caronamide alone, but this difference may only be a matter of chance.

4. Buffered penicillin given as above, together with a single dose of cremostaticin® (0.045 gm./lb.) to each of 10 patients, led to the best results. Table XIV shows average levels of 0.28, 0.69, 0.25 and 0.1 u./cc. at ½, 1½, 3 and 4½ hrs., respectively, with only 1 case failing to have a detectable level at 4½ hrs. These studies support the claims of previous workers that an antacid is of

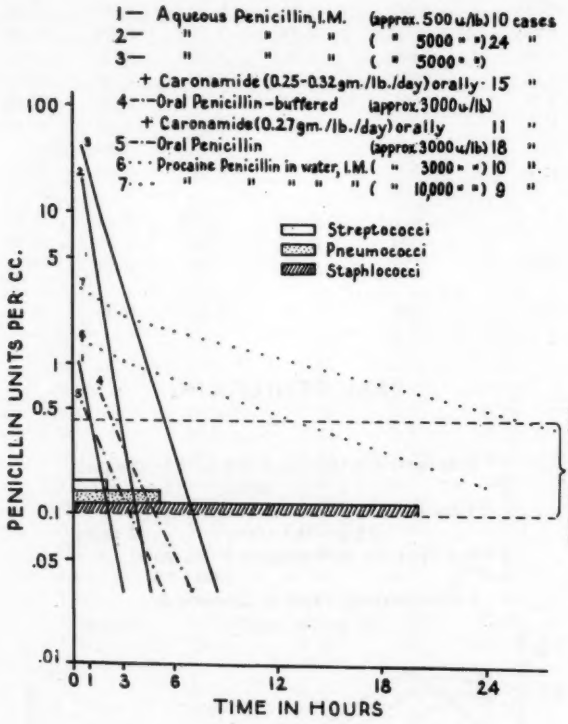
1— Aqueous Penicillin, I.M. (approx. 500 u./lb.) 10 cases
2— " " " (" 5000 " ") 24 "
3— " " " (" 5000 " ")
+ Caronamide (0.25-0.32 gm./lb./day) orally 15 "
4— Oral Penicillin-buffered (approx. 3000 u./lb.)
+ Caronamide (0.27 gm./lb./day) orally 11 "
5— Oral Penicillin (approx. 3000 u./lb.) 18 "
6··· Procaine Penicillin in water, I.M. (" 3000 " ") 10 "
7··· " " " " " (" 10,000 " ") 9 "
Streptococci
Pneumococci
Staphylococci
PENICILLIN UNITS PER CC.
100
10
5
1
0.5
0.1
.05
.01
0 1 3 6 12 18 24
TIME IN HOURS
Optimal bactericidal level

CHART 4

value in increasing the absorption of oral penicillin. Furthermore, in spite of the fact that 1 dose of caronamide might not achieve maximal tubular block, the addition of caronamide may be of value in this form of therapy. These results are summarized in Chart 3. It should be noted that the dosage of caronamide recorded in the figure is in terms of total daily dosage of 0.27 gm./lb./24 hrs. of which the single dose given in the experiment is a 1/6 aliquot or 0.045 gm./lb.

Comparison of Penicillin Regimes: Chart 4 is a graphic summary of the results just described. For ease of comparison, the optimal *in vitro* bactericidal level (0.1 to 0.4 u./cc.) and the time required for destruction of 99.9% of certain sensitive organisms are also marked on the chart.

DISCUSSION

In prescribing penicillin therapy, the clinician has now at his command a bactericidal agent of great therapeutic flexibility. This agent may be administered in various forms by

different routes or in combination with an enhancing agent. The choice of regimen to be prescribed and the combination to be used depend on the type of infection and the nature of the organisms involved. In the majority of instances where the infection is not severe and is due to a penicillin-sensitive organism, there is a wide choice of regimens, from any of which the clinical outcome will be, in all probability, equally satisfactory. The choice, then, will depend largely on such factors as convenience of administration and comfort of the patient. If, on the other hand, the patient is seriously ill or fails to respond satisfactorily to ordinary dosages, it is the responsibility of the clinician to investigate the possibility of the infecting organism being relatively resistant to penicillin or in a site not easily reached by the drug, as in the vegetations of subacute bacterial endocarditis or in an abscess. In this type of infection, a satisfactory result will not be obtained without due consideration of an adequate therapeutic program.

It seems important here to stress the fact that bacterial resistance to penicillin is a relative and not an absolute condition. Organisms reported as resistant may be resistant to concentrations of 0.1 u./cc., but susceptible to 1.0 u./cc. When, therefore, the patient with a bacterial infection does not respond to penicillin therapy as expected, such therapy should not of necessity be abandoned, but an exact measurement of *in vitro* resistance of the infecting organisms should be obtained, and an attempt made to raise the patient's plasma penicillin levels above the sensitivity level of the organism for a sufficient length of time. This is especially important in many types of staphylococcal infection and in subacute bacterial endocarditis.[34] King et al.[35] have achieved blood levels of from 96 to 128 u./cc. continuously for over eight hours, by using 10,000,000 u. in one liter of physiologic saline intravenously by slow drip, in combination with full doses of caronamide by mouth, and it would seem that almost any level could be obtained for almost any length of time by a suitable adjustment of amounts and intervals of penicillin, using caronamide to enhance the height of the blood level by delaying the rate of excretion.

The results obtained in this study confirm the theoretic consideration that the slow absorbing type of penicillin is not suitable for obtaining levels much over 1 to 2 u./cc., even when caronamide is used, since the rate of absorption is limited by design. For highly resistant organisms then, or for organisms protected in vegetations, relatively inaccessible body cavities or abscesses, the rapidly absorbed aqueous preparations should be used in large doses.

It seems clear from this study that oral penicillin is uneconomical from the point of cost of penicillin but, for the sake of convenience, may be given in mild illnesses and can, though less consistently, achieve levels comparable to those achieved by the intramuscular route. It is obvious that it should not be relied on in cases where the patient is failing to respond.

The foregoing discussion should not be construed into meaning that, under the circumstances discussed, other antibiotics should not be introduced into the therapy if appropriate, but only to mean that the best use should be made of the nontoxic, easily available penicillin, whether or not other antibiotic or chemotherapeutic measures are indicated.

Summary

A study was made of the blood levels and the clearance rates of penicillin that follow different doses and routes of administration of penicillin, in normal children from 2 to 11½ years with normal kidney function.

Following intramuscular injection of aqueous penicillin, optimal bactericidal levels (*cf.* Eagle and Musselman[2]) were obtained with a daily dose of 5000 u./lb. if given every three hours, or 10,000 u./lb. given every six to eight hours. If adequate doses of oral caronamide were added to the latter dosage scheme, the above levels could be obtained for 8 to 12 hours.

Procaine penicillin of the large particle size (procaine penicillin A) used in this study, when given in doses of 6000 u./lb., provides optimal bactericidal levels for 24 hours or more in some instances. Furthermore, the same dosage scheme using preparations of a smaller particle size (procaine penicillin B), which did not sustain bactericidal levels for quite as long, resulted in successful therapy on clinical trial. Caronamide added by mouth does not increase the initial height of the blood levels appreciably, but does delay the plasma penicillin clearance rate.

Oral penicillin is variable in its action. It appears to be more reliable if given in a buffered form and the addition of caronamide improves the levels obtained.

The therapeutic application of these different regimens is discussed.

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SPANISH ABSTRACT

Regimenes de Penicilina en la Práctica Pediátrica; Estudio de los Niveles de Sangre

Se hizo un estudio de las cantidades de sangre y de las proporciones de salida de penicilina que siguen a diferentes dosis y rutas de administración de penicilina en niños normales de 2 a 11-1/2 años de edad con función de riñón normal.

Después de la inyección intramuscular de penicilina acuosa, se obtuvieron las cantidades bactericidas optimas (cf., Eagle y Musselman[2]) con una dosis diaria de 5000 u./lb. si dada cada 3 horas, o 10,000 u./lb. dada cada 6 a 8 horas. Si adecuadas dosis de caronamide oral fueran agregadas al último plan de dosis, las cantidades de arriba podrían obtenerse por 8 o 12 horas.

La penicilina procaina de tamaño particula grande (penicilina procaina A) usada en este estudio, cuando administrada en dosis de 6000 u./lb., proporciona cantidades bactericides optimas por 24 horas o más en algunos casos. Además el mismo plan de dosis usando preparaciones de un tamaño de partícula más pequeño (penicilina procaina B), que no sostuvieron cantidades bactericidas por tanto tiempo, dió buenos resultados en la terapia en el ensayo clínico. El caronamide agregado por la boca no aumenta la altura original de los niveles de sangre de manera considerable, pero si dilata la proporción de salida de la penicilina plasma.

La penicilina oral es variable en su acción. Parece ser más segura si se da en una forma amortiguada y la adición de la caronamide aumenta la cantidad obtenida.

La aplicación terapeutica de estos regimenes diferentes es tratada.

1740 Bainbridge Street

CLINICAL EVALUATION OF ABNORMAL ENZYME CONTENT IN THE PANCREATIC JUICE OF CHILDREN

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THE PROCESS of identifying fibrocystic disease of the pancreas among the various conditions included in the celiac syndrome evolved slowly over the years 1913 to 1938, during which period only 11 articles were published, each describing one to three cases.[1-11] In 1938, Dorothy Andersen[12] clarified the diagnostic criteria for fibrocystic disease of the pancreas by conducting a clinical and laboratory analysis of a series of cases and demonstrating the now well-recognized changes in the enzyme activity of duodenal juice.

This present paper is a review and critical appraisal of the relationships between symptomatology and duodenal enzyme findings in 165 children who had or were suspected of having chronic intestinal disease or fibrocystic disease of the pancreas. These cases were seen between 1943 and 1947.

The children were referred for pancreatic enzyme study by the attending physicians and residents in charge of the patients. All patients referred for study were accepted. The series comprised: (1) children presenting the celiac syndrome; (2) children with chronic intestinal disorders not typical of the celiac syndrome; (3) children with diarrhea who did not respond to treatment in a reasonable length of time; (4) children whose clinical history and findings were suggestive of fibrocystic disease of the pancreas; (5) children with chronic or recurrent pulmonary disease; (6) children with marked malnutrition due to various causes.

PROCEDURE

Technic of Intubation: Most of the intubations were done with a single-lumen duodenal tube of the Levine type, with size adapted to the age of the child. The procedure employed was essentially that of Andersen.[12] If the tube was large enough and not too soft, introduction into the duodenum under the fluoroscope was accomplished easily, usually requiring only a few minutes or an hour at the most. Collection of a good specimen of duodenal juice unadulterated with gastric juice was the difficult part of the procedure. This occasionally required 2 or 3 hrs.

When yellow clear juice which was alkaline to nitrazine paper began to drain, it was collected in quantities of about 0.5 ml. in a series of test tubes. Each test tube was placed in ice immediately and kept cold. The quantity of juice in each tube was small, so that a sudden reappearance of gastric juice would not contaminate the entire sample. Mixture with gastric juice was detected either by a change in the gross appearance of the pancreatic juice or by a change in pH. An attempt was made to obtain specimens from the 2nd portion of the duodenum where the enzymic activity is the highest. Of the many small specimens collected, those which appeared clear, free from mucus, and the most alkaline to nitrazine paper, were combined to make up 1 specimen of 4 ml.

During the last weeks of the study, a double tube was used and found to be more consistently successful in preventing gastric contents from contaminating specimens drawn from the duodenum. The double tube consisted of 2 single Levine tubes tied together at intervals in such a way that, when in place, the tip of 1 tube lay in the duodenum, while the tip of the other reached only into the stomach.

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Continuous suction was applied to the tube in the stomach during the time that duodenal juice was draining from the other tube.

In working with adults, some investigators apply continuous suction to the duodenal tube as well as to the gastric tube, so that the rate of flow per minute can be measured. In the author's experience with children, however, the flow of duodenal juice has been found to be too spasmodic for measurement of rate.

Technic of Enzyme Testing: The chemical tests for activity of trypsin, lipase and amylase were started as soon as the juice was collected, using the methods outlined below.

Trypsin activity (method of Andersen and Early[14]) was determined by adding a known amount of melted gelatin to the same quantity of increasing dilutions of pancreatic juice in 5% sodium bicarbonate. Trypsin in juice when incubated at 37° C. for 1 hr. will digest gelatin so that the mixture no longer solidifies when put in the refrigerator. The end point was taken as the smallest amount of juice which liquefied the gelatin. Normal pancreatic juice will liquefy gelatine in amount of 0.02 ml. or less. In this paper when "no trypsin activity" is mentioned, it is meant that gelatin was not liquefied by the greatest amount of duodenal juice used in the test, *i.e.,* 3.2 ml.

Lipase activity (modification of the method of Cherry and Crandall[15]) was determined by adding 1.0 ml. of juice to 2.0 ml. of olive oil and 1.0 cc. of phosphate buffer of pH 7.0. The lipase activity

TABLE IA

GROUP I. PATIENTS WITH NO ENZYME ACTIVITY
(Fibrocystic Disease of Pancreas)

No.	Patient	Sex	Ages at time of this report	Ages at time of intubation	Dates of intubations	Enzyme Activity of Duodenal Juice			
						pH	Trypsin* in ml.	Lipase† in ml.	Amylase‡ in mg.
1	B.R.	F	5 mos. (d)	2½ mos.	8/ 8/45	8.0	No activity	0.5	25.1
2	C.M.	F	7 mos.	4 mos.	10/ 9/47	Alk.	" "	0.8	5.9
3	L.S.	F	7 mos.	4 mos.	10/ 8/47	6.2	" "	0.4	7.4
	L.S.				10/30/47	7.3	" "	0.7	0.0
4	H.P.	M	7 mos.	6 mos.	12/19/47	7.9	" "	4.6	0.6
5	R.B.	M	8 mos. (d)	4 mos.	6/ 5/46	7.1	" "	0.6	—
6	F.S.	F	8½ mos.	6½ mos.	11/17/47	7.1	" "	0.6	7.3
	F.S.				12/ 4/47	7.7	" "	0.4	6.0
7	A.V.	M	14 mos.	11 mos.	10/22/47	7.5	" "	0.6	1.3
8	R.S.	M	17 mos. (d) (a)	9½ mos.	4/ 9/46	7.1	" "	0.8	0.0
9	B.W.	F	18 mos. (d) (a)	8 mos.	12/27/44	7.3	" "	1.4	1.2
10	R.Z.	M	19 mos.	7 mos.	1/22/47	7.2	" "	0.3	0.0
	R.Z.			8 mos.	2/26/47	7.4	" "	0.6	0.4
	R.Z.		28 mos. (d) (a)	16½ mos.	11/12/47	7.4	" "	0.5	12.1
11	J.R.	M	20 mos. (d)	4 mos.	8/ 9/45	6.2	" "	1.9	0.2
12	P.G.	M	20 mos.	10 mos.	3/ 6/47	7.9	" "	0.1	0.1
	P.G.			17 mos.	10/ 9/47	8.1	" "	0.9	0.1
13	A.B.	F	2½ yrs.	2 yrs.	7/31/47	8.0	" "	0.8	30.0
	A.B.				8/13/47	7.3	" "	2.0	13.5
14	T.V.	M	2½ yrs.	9 mos.	3/12/46	6.6	" "	2.9	0.0
15	S.S.	F	2½ yrs. (d)	2 yrs.	8/15/46	7.2	" "	—	0.3
16	G.K.	F	3 yrs.	10 mos.	12/ 6/45	7.1	" "	1.7	0.0
17	M.L.	F	4½ yrs.	4 yrs.	6/ 4/47	7.7	" "	1.6	0.1
18	C.B.	F	4½ yrs. (d)	3½ yrs.	1/28/47	7.9	" "	0.5	4.8
19	J.B.	M	6 yrs.	5 yrs.	2/12/47	8.2	" "	0.3	0.2
20	R.P.	M	6 yrs.	3 yrs.	1/31/45	7.2	" "	0.1	0.3
21	E.H.	F	7½ yrs.	6½ yrs.	2/19/47	7.0	" "	0.9	25.6
22	J.C.	F	9 yrs. (d)	8½ yrs.	8/28/46	Alk.	" "	0.3	17.8
23	S.T.	F	Living ?	2½ yrs.	8/23/44	7.0	" "	1.9	16.4

* Trypsin activity is expressed as the number of ml. of duodenal juice necessary to liquefy 2 ml. of 7.5% gelatin. Normal juice will liquefy the gelatin in amounts of .02 ml. or less.

† Lipase activity is expressed as the number of ml. of 0.1 N NaOH necessary to neutralize the fatty acids produced by the action of 0.1 ml. of duodenal juice on 2.0 ml. of olive oil. The normal value is 10.0 ml. or more.

‡ Amylase activity is expressed as the number of milligrams of equivalent glucose produced by the action of 1.0 ml. of a 1:50 dilution of duodenal juice on a 1% starch solution. The normal value is 20 mg. or more for individuals over 9 mos. of age.

(d) Age at death

(a) Autopsy

TABLE IB

Clinical Features of Patients in Group I

No. of patient	Name of patient	Malnutrition	Appetite	Stools bulky, foul, or loose	Stools contained excess fat	Age of onset of lower respiratory infection	Chest roentgenograms compatible with pancreatic fibrosis	Other anomalies or clinical disorders in patient	Total no. of siblings	Illness in siblings
1	B.R.	+++	Poor	+	+	10 days	+	0	0	—
2	C.M.	++++	Good	+	+	4 wks.?	+	0	0	—
3	L.S.	++	Good	+	+	4 wks.	+	0	4	One died at 3 mos. of pneumonia; one living: has chronic hacking cough
4	H.P.	+++	Good	+	+	6 wks.	Broncho-pneumonia	0	2	One died at 3 mos. of diarrhea; one 4½ yrs. living and well.
5	R.B.	++++	Good	+	+	3 mos.	+	0	0	—
6	F.S.	++	—	+	+	2 mos.	+	0	1	None
7	A.V.	++++	—	+	+	Birth	+	0	1	None
8	R.S.	+++	Good	+	+	6 mos.	+	0	1	None
9	B.W.	++++	Poor	+	Not checked	4 mos.	+	0	1	None
10	R.Z.	++++	Poor	+	+	6 mos.	+	0	0	—
11	J.R.	None	Good	+	Not checked	Before 3 mos.	+	0	3	One died of bronchopneumonia at 15 mos.
12	P.G.	++++	Poor	+	+	4½ mos.	+	0	2	None
13	A.B.	+	Good	+	+	13 mos.	Broncho-pneumonia	(1) Recurrent rectal prolapse (2) Hemangiomata	?	Patient adopted
14	T.V.	+++	Good	+	+	4 mos.	+	0	1	None
15	S.S.	+++	Fair	+	—	15 mos.	+	0	Not known	
16	G.K.	++++	—	+	+	2 mos.	+	0	2	None
17	M.L.	++	Good	+	+	12 mos.	+	0	1	One with repeated U.R.I. and bronchitis; roentgenograms compatible with fibrocystic disease
18	C.B.	++++	—	+	+	—	+	0	2	One still birth. One is pt. J.B. below.
19	J.B.	+++	—	+	—	—	—	0	2	One still birth. One is pt. C.B. above.
20	R.P.	None	—	+	+	2½ yrs.	+	Rectal prolapse	0	—
21	E.H.	+++	—	Norma	+	Early mos.	+	Congenital bands with partial obstruction of colon	0	—
22	J.C.	++++	Poor	Normal	+	Birth	+	0	2	One child died at 7 mos. with symptoms of wasting and chronic cough since birth. One child living, has chronic cough and wasting.
23	S.T.*	None	Good	+	Not checked	3 mos.	+	0	0	—

* May not be living. Unable to follow patient. Had chronic purulent bronchitis with recurrent pneumonia 1½ yrs. ago at age of 3½ yrs.

is reported as the number of ml. of 0.1 N sodium hydroxide needed to neutralize the fatty acids formed during 24 hr. incubation at 37° C.

Amylase activity (modification of the method of Free and Meyers[16]) was determined by incubating a mixture of 1.0 ml. of juice (diluted 1:50 with a phosphate buffer of pH 7.2), and 1.0 ml. of 0.5 M NaCl with 6.0 ml. of a 1% starch solution for 30 min. at 37° C. The amount of glucose which formed from the starch by the action of amylase was measured by the picric acid method of Free and Meyers. A blank was run and its value subtracted from the unknown to correct for the small amount of glucose contained in starch. The amylolytic activity is reported in terms of the number of milligrams of glucose equivalent formed. The normal level is 20 mg. or more for infants over 9 mos. of age. Under this age, the amylase activity of pancreatic juice is normally low.

All the tests in this series of cases were performed with the same laboratory technics and should be comparable.

Classification of Cases

Correlations were made between the clinical disturbances exhibited by the 165 children and the results of the study of their pancreatic secretions. Of the 165 patients, 76 cases have not been analyzed further since they showed normal potency of all the pancreatic enzymes and a variety of clinical conditions apparently unrelated to disturbance of pancreatic secretions. About 60% of these had been intubated because of chronic or recurrent lower respiratory infections.

Of the 89 remaining patients, 71 showed a diminished or absent content of 1 or more of the 3 major pancreatic enzymes. The other 18 patients had normal pancreatic juice but were included in the study as examples of extreme malnutrition. Scrutiny of the clinical features of these patients in relation to their pancreatic juice findings led to their being grouped under 5 headings: (1) those whose pancreatic juice showed only a trace of enzyme activity and whose clinical histories were typical of fibrocystic disease of the pancreas; (2) individual patients of special interest whose duodenal juice resembled that of patients in group 1 but with certain points of contrast; (3) those with a partial reduction of all enzyme activity; (4) those whose juice was deficient in only 1 of the 3 enzymes; (5) those with normal enzymes but who were severely malnourished.

Group I: Patients with No Enzyme Activity: Fibrocystic Disease of the Pancreas (Tables IA and IB): Twenty-three children belong to the first group and fulfill the criteria for diagnosis of fibrocystic disease of the pancreas. Fifteen are still living and range in age from 6 mos. to 7 yrs. One child (Patient No. 23) has moved away and cannot be located; when last heard from 1½ yrs. ago, she was 3½ yrs. old and in poor condition, having just recovered from a recurrence of severe bronchopneumonia. Eight of the group have died. Autopsy performed on 3 of these confirmed the diagnosis of fibrocystic disease of the pancreas in each case.

Trypsin activity was absent in all 23 children. Some had a trace of lipase activity which was probably due to enzymes from outside the pancreas. Amylase activity was present in trace amounts in all but 7 patients who had higher or even normal levels. The results for amylase may be misleading, however, due to the technical difficulties peculiar to obtaining juice from children with this disease. In pancreatic fibrosis with advanced purulent bronchitis, the stomach contents are extremely profuse and frequently have a pH above 7.0, probably due to the swallowed secretions from the lungs and salivary glands. Since, in these patients, it is even more difficult than usual to collect pancreatic juice undiluted with gastric contents, the amylolytic activity may come from swallowed salivary secretions which pass through the alkaline stomach without being inactivated. Malnutrition was present in all but 1 patient. Appetite was variable, ranging from poor to good. Only 2 children had a history of normal stools and even these had excess stool fat on examination. Roentgenograms of the chest revealed typical bronchopneumonia, *i.e.*, had diffuse patchy densities resulting from the multiple small areas of pneumonitis and bronchiectasis so frequently found in fibrocystic disease of the pancreas. These findings are well described by Atwood and Sargent.[17] Six of these children have siblings with histories suggestive of the same disease.

Group II: Patients with No Enzyme Activity: Pancreatic Deficiency with Atypical Features (Table II): These 2 children, like those of Group I, had duodenal juice which contained no trypsin, a trace of lipase and variable amylase. They might have been included with Group I except that there were certain atypical features associated with their disease. Therefore, they will be discussed separately.

1. A. L., now 9½ yrs. old, was normal until 7 mos. of age, when he developed a bowel obstruction which was relieved with difficulty but without surgery. Starting with this episode, he developed a large abdomen and bulky foul stools. This condition continued throughout his life, in spite of a

low fat diet which was prescribed for him at the age of 2 yrs. He has never had a cough and, except for an occasional cold, he has never had a respiratory infection. Chest roentgenograms were negative. After his 1st enzyme studies at the age of 8½ yrs., a diagnosis of pancreatic fibrosis was made. He was then given a high protein diet and pancreatin. Now, at the age of 9½ yrs., his stools have improved remarkably, his abdomen has reduced in size, and he has gained 6.4 kg. in wt. Three intubations within 15 mos. revealed essentially the same type of duodenal juice.

The history of this patient (A. L.) contains evidence of the presence of pancreatic deficiency since the age of 7 mos. He has lived for 9½ yrs. without having had pulmonary infection of any kind. This is in striking contrast to all of the children in Group I who developed respiratory disease at an early age. A. L., although underweight, has lived a normal life, being exposed to all of the usual infections in school. He may have normal mucous secretions from the lungs, salivary and secretory glands of his gastrointestinal tract. If so, the pathology in this child is limited to the pancreas, which differentiates

TABLE II

GROUP II. PATIENTS WITH NO TRYPSIN ACTIVITY
(Pancreatic Deficiency with Atypical Features)

No.	Patient	Age at intubation	Dates of intubations	Enzyme Activity of Duodenal Juice			
				pH	Trypsin* in ml.	Lipase† in ml.	Amylase‡ in mg.
1	A.L.	8½ yrs.	7/18/46	7.5	No activity	0.0	5.0
			7/23/46	6.7	No activity	0.4	0.0
		9½ yrs.	10/27/47	7.5	No activity	0.0	15.7
3	G.L.	5 wks.	11/ 5/46	7.5	No activity	1.3	8.5

* Trypsin activity is expressed as the number of ml. of duodenal juice necessary to liquefy 2 ml. of 7.5% gelatin. Normal juice will liquefy the gelatin in amounts of .02 ml. or less.

† Lipase activity is expressed as the number of ml. of 0.1 N NaOH necessary to neutralize the fatty acids produced by the action of 0.1 ml. of duodenal juice on 2.0 ml. of olive oil. The normal value is 10.0 ml. or more.

‡ Amylase activity is expressed as the number of milligrams of equivalent glucose produced by the action of 1.0 ml. of a 1:50 dilution of duodenal juice on a 1% starch solution. The normal value is 20 mg. or more for individuals over 9 mos. of age.

him from those of Group I. Among other theories of etiology possible for this type of case, 2 are attractive. One is that he may have an anomalous pancreas, perhaps stenosis of the ducts. Secondly, it is possible that there has been an infection of unknown etiology involving the pancreas either in intrauterine life or during the 1st 7 mos. of his life.

2. G. L. was an infant who weighed 3.2 kg. at birth, following a normal delivery and a normal full term pregnancy of a healthy mother. He had poor muscular tone and his cry was not audible until the 14th day of life. From the 1st day he refused to take feedings and when forced he vomited. Stools were normal until the 16th day, when he began to have 5 or 6 slightly loose stools daily. Examination revealed excess stool fat. Occasional vomiting persisted but refusal of feedings became less. He had 1 period of severe diarrhea. When intubated at 5 wks., he was found to have duodenal juice without enzyme activity. The juice was thick, ropy, and brownish in color, typical of many patients with fibrocystic disease of the pancreas. The child was then given pancreatin with each feeding and amino acids were added to his milk. In spite of this, he failed to gain weight. Diarrhea recurred. When he died at the age of 3 mos., he weighed 2.9 kg. Autopsy revealed no cause for death. The pancreas and lungs were reported as normal. However, sections of the pancreas were examined by several pathologists, one of whom felt that there was inspissated material in the finer acini as well as in the small ducts of the type described by Farber.[18] This patient may belong to a small group of children who, Farber feels, are examples of true pancreatic insufficiency due to inspissated secretion. Pancreatic atrophy and fibrosis had not yet developed.

Group III: Patients with Transitory Reduction of All Three Enzymes (Table III): There are 5

TABLE III

GROUP III. PATIENTS WITH TRANSITORY REDUCTION OF TRYPSIN

No.	Patient	Age at intubation	Dates of intubations	Enzyme Activity of Duodenal Juice			
				pH	Trypsin* in ml.	Lipase† in ml.	Amylase‡ in mg.
1	W.L.	20 mo.	11/18/43	7.4	0.16	6.2	0.6
		22 mo.	1/12/44	7.4	0.08	8.3	2.0
		2½ yrs.	10/25/44	—	splenectomy		
		5 yrs.	11/ 3/47	7.5	0.02	10.9	25.0
2	R.R.	8 mo.	1/19/44	7.9	0.04	5.1	10.7
		4 yrs.	11/ 7/47	7.0	0.005	12.6	21.4
3	S.J.	19 mo.	8/26/46	7.4	0.04	0.7	31.4
		33 mo.	11/ 4/47	7.7	0.005	9.2	25.0
4	J.K.	6 yrs.	12/ 4/47	7.8	0.04	12.1	12.0
5	C.R.	6 yrs.	12/19/46	7.3	No activity	—	20.0
			12/30/46	7.2	No activity	1.2	14.3
		7 yrs.	9/ 4/47	7.3	0.04	6.5	31.5

* Trypsin activity is expressed as the number of ml. of duodenal juice necessary to liquefy 2 ml. o 7.5% gelatin. Normal juice will liquefy the gelatin in amounts of .02 ml. or less.

† Lipase activity is expressed as the number of ml. of 0.1 N Na OH necessary to neutralize the fatty acids produced by the action of 0.1 ml. of duodenal juice on 2.0 ml. of olive oil. The normal value is 10.0 ml. or more.

‡ Amylase activity is expressed as the number of milligrams of equivalent glucose produced by the action of 1.0 ml. of a 1:50 dilution of duodenal juice on a 1% starch solution. The normal value is 20 mg. or more for individuals over 9 mos. of age.

children in this group. The 1st 4 had a partial reduction of trypsin activity. These 4 are the only patients in the study who did not have either normal or absent trypsin on first intubation. In 3 of these (except J. K.), lipase was also reduced, and amylase activity was reduced in 3 others (except S. J.). Since S. J. had an achlorhydria, the amylolytic activity of the duodenal juice might have been due to contamination with salivary amylase. The common factor in this group is a partial reduction of tryptic activity along with that of at least 1 other enzyme. The 5th and last child in the group had no trypsin; only a trace of lipase and reduced amylase were found in the juice from her 1st 2 intubations, but 8 mos. later a study of her enzymes revealed a partial return of trypsin so that her juice gave a picture similar to those of the 1st 4 patients in this group. Like the patients W. L., R. R. and S. J., the lipase was also reduced and, like S. J., the amylase level was normal, perhaps also due to contamination by salivary amylase. The clinical picture of each of these patients is quite distinct.

1. W. L., at the age of 10 mos., was found to have familial hemolytic jaundice with anemia and hepatosplenomegaly, He required multiple transfusions to keep him alive. At 1 yr., he developed a large abdomen and an increase in the number of daily stools. At 1½ years, he had diarrhea. One month later, the stools were recorded as greenish, bulky and foul. His first intubation, done when he was 20 mos. of age and in poor physical condition, showed reduction of tryptic digestion together with that of lipase and amylase; the 2nd, when his condition had been improved by a high protein, low fat diet and transfusions, but was still only fair, showed improved activity of all 3 enzymes. When he was 3 yrs. old, splenectomy was performed, which was followed by a remarkable improvement. For the 2 yrs. before his last intubation, his health had been excellent; blood count had remained normal and stools were normal on a normal diet. On this last intubation, the activity of all 3 enzymes had returned to normal.

2. R. R. had been vomiting frequently since birth. He had large, firm, odorous stools. In spite of

an excellent appetite, he gained weight slowly, so that when intubation was done at the age of 8 mos., he had a large abdomen, wasted extremities, and weighed only 5.6 kg. At this time he had moderate reduction in the activity of all 3 enzymes. Many types of treatment had been unsuccessful until he was given a high protein diet. Amino acids added to his formula brought about immediate improvement. The child ceased vomiting and began to gain in weight. Intubation was not repeated until he was 4 yrs. of age, when he was found to be in good physical condition and normal in height and weight. His enzyme activity had also returned to normal.

3. S. J. had recurrent diarrhea and was also a behavior problem. Thinking her symptoms due to allergy, her family physician had denied her milk and other foods for several months before her first intubation, which revealed a moderate decrease in the activity of trypsin and lipase. When returned to a normal diet, her diarrhea stopped, and after 14 mos. of good health the enzyme activity of her pancreatic juice had returned to normal.

4. J. K. had had bronchiectasis with chronic infection for 1½ yrs., when the enzyme studies were done. Throughout her illness, the stools were normal in appearance and examination of 1 stool specimen taken later revealed no excess fat. Treatment with penicillin, streptomycin and sulfonamides, including aerosol penicillin and streptomycin, brought about improvement. She was in fairly good physical condition when intubation was done which, however, revealed a moderate decrease in trypsin and amylase activity. She was considered almost ready for lobectomy when she developed bilateral pneumonia. Culture of bronchoscopic aspirations revealed 1 organism repeatedly, B. pyocyaneus. This was resistant to chemotherapy and she died 7 mos. after the 1 enzyme study was done. Autopsy was not permitted.

5. C. R., 7 yrs. old, had had recurrent bronchitis with asthmatic wheezing since infancy. During the last 2 yrs. prior to examination, she had had chronic sinusitis. At 6 yrs. and 3 mos. of age, it was discovered, on 2 intubations, that she had no pancreatic enzyme activity, and it was thought that she had fibrocystic disease of the pancreas. She was treated for her respiratory infection and given a high protein low fat diet with pancreatin. During the summer she improved remarkably. Her nutrition became excellent. When intubation was repeated 8 mos. after the previous examination, it was found that her pancreas was now functioning, *i.e.*, her pancreatic juice contained active digestive enzymes. Although the results were not up to normal levels, the levels of activity were similar to those found in the other 4 children of this group at the time of their first examination, *i.e.*, partially reduced.

Among the children of this group there is no common clinical pattern. However, ill health from various causes was associated with a common suppression of the activity of trypsin and at least 1 other enzyme. Following recovery, in the 1st 3 patients, the enzyme activities reverted to normal. In the 4th patient, repeated studies were not obtained before her death. When first tested, the 5th child, C. R., had no trypsin and only a trace of lipase activity, which placed her in Group I with patients having fibrocystic disease of the pancreas. Eight months later, when she had returned to apparent good health, her enzyme activity had improved, so that trypsin and lipase were only partially reduced. She had a complete but temporary suppression of pancreatic enzymes, apparently as a result of her respiratory infection. This is unusual. She is the only example in this series, and Andersen[19] reported none in her work. However, Véghelyi[20] reported 3 such cases in July 1947. He found temporary pancreatic insufficiency following 2 cases of mumps and 1 of scarlet fever. All of them recovered pancreatic function later. Andersen[18] has found that dehydration such as that which accompanies acidosis in the celiac crisis may temporarily lower the amount of pancreatic enzymes secreted. However, in the patients reported here, dehydration was not noticeably present. In the diagnosis of fibrocystic disease of the pancreas, therefore, the absence of trypsin activity is strong evidence but not pathognomonic of the disease.

Group IV: Patients with Reduced Activity of a Single Enzyme: *A. Reduced Activity of Lipase Alone:* Twenty-five children were found who had reduced lipase activity in the presence of normal trypsin and amylase on their first intubation. They could be divided into 3 groups clinically. Twenty of them had some type of gastrointestinal disorder; 4 had respiratory diseases without gastrointestinal symptoms (although 2 had stools containing excess fat) and 1 child had cirrhosis of the liver, with jaundice.

It was possible to repeat the enzyme determinations on 16 of these children. The results of their tests are listed in Table IV. The patients are classified according to their previous clinical conditions and represent much the same proportion of gastrointestinal disorders to respiratory conditions

TABLE IV

GROUP IV (a). PATIENTS WITH REDUCED ACTIVITY OF LIPASE ALONE

No.	Patient	Age at intubation	Dates of intubations	Enzyme Activity of Duodenal Juice				Clinical condition of patient
				pH	Trypsin* in ml.	Lipase† in ml.	Amylase‡ in mg.	
Gastrointestinal Disorders								
A. Recurrent abdominal pain								
1	J.F.	11 yrs.	7/ 3/ 46	7.0	0.005	8.7	32.2	Giardiasis.
			9/17/47	6.8	0.005	18.3	24.0	Recovered from atabrine therapy.
2	K.W.	5 yrs.	6/25/46	7.4	0.02	2.0	26.9	Etiology unknown. Clay stools.
			12/31/47	7.0	0.005	15.4	30.2	Recovered.
3	C.S.	3 yrs.	6/25/45	6.6	0.005	1.8	29.0	Etiology unknown. Clay stools.
			9/ 2/47	7.0	0.005	10.5	23.8	Recovered.
4	R.M.	6½ yrs.	8/ 6/47	7.5	0.01	2.4	27.4	Etiology unknown. Clay stools.
			12/16/47	7.7	0.02	10.6	20.0	Recovered.
B. Frequency of stools								
5	D.W.	3 mos.	7/ 7/46	6.8	0.02	3.1	12.2	Parenteral diarrhea.
			10/10/47	7.4	0.005	12.1	24.2	Recovered.
6	J.W.	10 mos.	6/12/46	7.4	0.005	5.7	25.6	Milk allergy. Excess stool fat.
			9/30/47	7.0	0.005	9.9	22.3	Recovered.
7	E.H.	8 mos.	7/10/46	7.2	0.01	3.4	0.3	Etiology unknown.
			10/21/47	7.3	0.005	19.4	7.4	Recovered.
8	H.B.	1 yr.	9/26/45	Alk.	0.005	1.0	29.3	Etiology unknown. Excess stool fat.
			10/16/47	7.2	0.01	9.2	31.6	Recovered. Still poorly nourished.
9	R.L.	4 yrs.	4/30/46	7.0	0.005	0.9	27.9	Etiology unknown. Excess stool fat.
			10/ 3/47	7.0	0.005	7.9	35.0	Partially recovered. Still large stools.
10	F.R.	14 mos.	12/ 5/45	7.0	0.005	3.8	9.3	Celiac disease.
			11/ 5/47	7.5	0.01	12.0	14.0	Recovered.
11	J.P.	2 yrs.	3/13/47	7.0	0.01	6.5	25.6	Celiac disease.
			9/ 7/47	7.7	0.005	11.4	42.6	Recovered.
12	E.B	16 mos.	7/12/46	6.8	0.04	1.0	31.9	Celiac disease.
			9/ 3/46	Alk.	0.005	2.9	20.3	Celiac disease.
			10/31/47	7.3	0.01	8.9	30.0	Almost recovered.
13	M.B.	3 yrs.	10/ 9/46	7.5	0.01	2.1	25.4	Asthma plus celiac syndrome.
			6/13/47	7.4	0.01	8.3	30.8	Improved.
			10/14/47	7.5	0.005	13.1	32.0	Recovered.
Respiratory Diseases								
14	A.D.	3 yrs.	10/23/46	7.7	0.01	6.0	24.5	Asthma. Negative stool history, but excess stool fat.
			10/20/47	7.9	0.005	18.8	32.0	Recovered.
15	R.A.	9 yrs.	11/ 6/46	7.4	0.01	7.4	25.6	Recurrent bronchitis. Stools negative for excess fat.
			10/15/47	7.3	0.005	10.4	32.3	Recovered.
16	R.O.	5 yrs.	9/24/46	7.2	0.02	4.6	32.0	Chronic pneumonitis. Stools not examined.
			10/28/47	7.5	0.005	4.0	25.5	Chronic pneumonitis—severe.

* Trypsin activity is expressed as the number of ml. of duodenal juice necessary to liquefy 2 ml. of 7.5% gelatin. Normal juice will liquefy the gelatin in amounts of .02 ml. or less.

† Lipase activity is expressed as the number of ml. of 0.1 N NaOH necessary to neutralize the fatty acids produced by the action of 0.1 ml. of duodenal juice on 2.0 ml. of olive oil. The normal value is 10.0 ml. or more.

‡ Amylase activity is expressed as the number of milligrams of equivalent glucose produced by the action of 1.0 ml. of a 1:50 dilution of duodenal juice on a 1% starch solution. The normal value is 20 mg. or more for individuals over 9 mos. of age.

as that found in the original larger group from which they were drawn. It may be seen that in every case, at the time of the first intubation, the lipase activity of the pancreatic juice was considerably lower than normal, ranging from 0.9 cc. to 8.7 ml. (The normal level is 10 ml. or more.) At the time the enzyme determinations were repeated, 12 of the 16 children were in good health, having normal stools. Their pancreatic juice had also regained its normal enzyme activity, as shown in the table. The other 4 children, Nos. 8, 9, 12 and 16, still presented some symptoms and still had some reduction in lipase activity. Patient No. 8, H. B., remained undernourished and ate poorly, but had

normal stools. Her lipase activity showed marked improvement but had not yet reached normal levels at the time of her last examination. Patient No. 9, R. L., was well clinically, but according to his mother still had large soft stools. Lipase activity was still slightly reduced. Patient No. 12, E. B., had had typical celiac disease. Following the usual regime, her physician had put her on a normal diet a month or so before her last intubation. Her stools were still somewhat large, soft and foul, but they were no longer frequent. At her last examination, the lipase activity, though much improved, was still a little below normal. Patient No. 16, R. O., was the only child who continued to be sick. He was a 7 yr. old boy who had had a chronic pulmonary infection for over 4 yrs., and

TABLE V

GROUP IV (c). PATIENTS WITH REDUCED ACTIVITY OF AMYLASE ALONE

No.	Patient	Age at intubation	Enzyme Activity of Duodenal Juice				Clinical condition
			pH	Trypsin* in ml.	Lipase† in ml.	Amylase‡ in mg.	
1	E.A.	2 yrs.	7.5	0.005	17.2	12.3	Celiac disease.
2	D.H.	11 mo.	7.3	0.02	14.7	4.8	Celiac disease.
3	B.C.	1 yr.	6.9	0.005	12.0	9.2	Celiac disease.
4	C.P.	1 yr.	7.0	0.01	15.5	13.9	Celiac disease.
5	D.L.	17 mo.	7.3	0.005	13.9	15.7	Celiac disease.
6	L.B.	1 yr.	7.1	0.005	13.9	15.2	Celiac disease.
7	R.R.	14 mo.	7.7	0.005	9.8	3.3	Frequent stools: Etiology unknown.
8	M.W.	15 mo.	7.2	0.005	13.0	2.9	Parenteral diarrhea.
9	A.K.	2 yrs.	7.3	0.005	9.8	11.1	Behavior problem.
10	E.M.	11 mo.	7.4	0.005	18.4	15.2	Food allergy.
11	A.W.	15 mo.	7.4	0.005	20.0	15.6	Food allergy.
12	L.S.	2 yrs.	6.8	0.005	10.4	14.0	Food allergy.
13	B.C.	8 yrs.	6.4	0.005	20.0	15.6	Abdominal pain: Etiology unknown.
14	E.F.	7 yrs.	7.3	0.005	20.2	17.4	Abdominal pain: Etiology unknown.
15	J.D.	5 yrs.	7.1	0.005	12.0	12.5	Hypophyseal tumor.
16	E.G.	5 yrs.	7.1	0.005	12.4	12.5	Melena.

* Trypsin activity is expressed as the number of ml. of duodenal juice necessary to liquefy 2 ml. of 7.5% gelatin. Normal juice will liquefy the gelatin in amounts of .02 ml. or less.

† Lipase activity is expressed as the number of ml. of 0.1 N NaOH necessary to neutralize the fatty acids produced by the action of 0.1 ml. of duodenal juice on 2.0 ml. of olive oil. The normal value is 10.0 ml. or more.

‡ Amylase activity is expressed as the number of milligrams of equivalent glucose produced by the action of 1.0 ml. of a 1:50 dilution of duodenal juice on a 1% starch solution. The normal value is 20 mg. or more for individuals over 9 mos. of age.

now had constant dyspnoea with cyanosis. His chest roentgenograms have been reported to be compatible with fungus infection but the diagnosis has not been confirmed by culture. His lipase activity was 4.0 ml., which was almost identical with the activity reported 13 mos. previously.

Therefore, among these patients, the lipase activity of the pancreatic juice roughly coincided with the clinical picture. Only 1 among the 16 children continued to be sick and was the only child whose lipase activity was still markedly suppressed when the tests were repeated. The possibility of technical error cannot be entirely ruled out, since in most of these patients only a single determination was made at each period of progress, and methods for lipase determinations are particularly liable to technical difficulties. However, when the tests are done by the same person on fresh juice with tested lots of olive oil, as these were, reasonably reproducible results can be obtained.

B. Patients with Reduced Activity of Trypsin Alone: There were no children in the whole study who had reduced trypsin activity in the presence of normal lipase and amylase. Such cases must be rare. Farber, Schwachman and Maddock[23] reported 1 case.

C. Patients with Reduced Activity of Amylase Alone: (Table V): Children under 9 mos. of age were not included in this group, in view of the normally low pancreatic amylase in young infants. Of the remaining patients, there were 16 who had reduced amylase activity in conjunction with normal trypsin and lipase. Six of them had idiopathic celiac disease. The other 10 children had unrelated conditions, although most of them had gastrointestinal complaints. Andersen[22] has reported that pancreatic juice of all children with celiac disease contains only a negligible amount of

TABLE VI

GROUP V. PATIENTS WITH NORMAL ENZYME ACTIVITY COINCIDENT WITH MALNUTRITION

No.	Patient	Birth wt.	Age at intubation	Wt. when intubated	Enzyme Activity of Duodenal Juice				Clinical Condition
					pH	Trypsin* in ml.	Lipase† in ml.	Amylase‡ in mg.	
1	J.L.	5′ 6″	2 mos.	6′12″	7.4	0.01	16.8	0.1	Cervical adenitis.
2	J.M.	6′10″	7 wks.	6′ 4″	6.6	0.005	12.0	0.7	Purulent ethmoiditis.
3	F.F.	7′10″	10 wks.	9′ 4″	7.6	0.01	15.0	1.1	Diarrhea.
4	J.M.B.	5′ 8″	3 mos.	7′ 4″	7.2	0.005	11.6	0.9	Feeding problem.
5	W.M.	7′11″	3 mos.	7′ 8″	7.0	0.01	16.7	3.1	Feeding problem.
6	A.S.	7′ 1″	3 mos.	8′10″	7.2	0.005	16.8	2.4	Epidemic diarrhea of newborn.
7	J.B.	5′13″	3 mos.	6′14″	7.5	0.01	15.5	2.4	Feeding problem.
8	C.K.	6′ 8″	3 mos.	8′ 2″	6.8	0.005	9.7	0.9	Epidemic diarrhea of newborn.
9	A.W.	8′ 6″	3½ mos.	8′ 4″	7.4	0.005	11.8	0.7	Feeding problem.
10	S.P.	7′ 6″	4 mos.	10′ 0″	7.4	0.005	15.2	2.9	Diarrhea.
11	R.D.	7′10″	4 mos.	9′ 0″	7.4	0.01	13.7	0.5	Epidemic diarrhea of newborn.
12	El.F.	6′ 2″	5 mos.	9′ 4″	7.0	0.005	10.6	10.2	Feeding problem.
13	Ed.F.	7′ 2″	5 mos.	10′ 2″	7.1	0.005	10.5	14.2	Feeding problem.
14	P.B.	8′ 5″	6 mos.	11′ 0″	6.7	0.01	13.3	2.1	G.I. disorder; etiology unknown.
15	J.R.	5′13″	6 mos.	7′ 7″	7.3	0.005	16.5	7.3	Feeding problem.
16	W.H.	—	2 yrs.	19′	7.7	0.005	17.2	22.3	Rheumatic arthritis.
17	R.S.	—	3 yrs.	24′	7.6	0.005	20.0	20.3	Hemolytic anemia.
18	M.V.	6′ 8″	3½ yrs.	28′	7.4	0.01	18.5	20.1	Anorexia: etiology unknown.

* Trypsin activity is expressed as the number of ml. of duodenal juice necessary to liquefy 2 ml. of 7.5% gelatin. Normal juice will liquefy the gelatin in amounts of .02 ml. or less.

† Lipase activity is expressed as the number of ml. of 0.1 N NaOH necessary to neutralize the fatty acids produced by the action of 0.1 ml. of duodenal juice on 2.0 ml. of olive oil. The normal value is 10.0 ml. or more.

‡ Amylase activity is expressed as the number of milligrams of equivalent glucose produced by the action of 1.0 ml. of a 1:50 dilution of duodenal juice on a 1% starch solution. The normal value is 20 mg. or more for individuals over 9 mos. of age.

amylolytic activity. However, in our group, except for 1 child (D. H.), whose amylase was low, the 6 children with celiac disease had amylase levels which were not greatly depressed below normal. In Group IV (a), Table IV, there were 3 children with celiac disease, 2 of whom had low lipase only and 1 of whom had a reduction in both amylase and lipase. Also, there were 6 children in this study not charted who had typical idiopathic celiac disease with normal pancreatic enzymes. This makes a total of 15 children over 9 mos. of age with celiac disease, of whom only 7 had a low level for amylase activity. Andersen states that in celiac children more than minimal values for amylase are due to contamination of pancreatic juice with salivary amylase. Since patients with this disease have achlorhydria, amylase from the salivary glands may pass through the stomach without being inactivated. In our study, all the children with celiac disease were intubated before the introduction of the double tube technic, so that contamination with salivary amylase was possible.

Group V: Patients with Normal Enzyme Activity Coincident with Malnutrition: (Table VI): In this study, there were 18 children who were examples of extreme malnutrition. Their birth weights and weights at the time of intubation are charted for comparison, in order to demonstrate this. The clinical cause of malnutrition is also listed for each patient. All of them had pancreatic juice which was normal for trypsin, lipase and amylase activity, according to the tests. The children of this group

were included because of the repeated statement that malnutrition causes a suppression of enzyme activity.[20,22,23] However, the study of the patients listed above indicates that this condition in itself need not cause reduced secretion of pancreatic enzymes.

Discussion

Pancreatic enzyme activity for trypsin, lipase and amylase was determined for 165 patients. The clinical condition of each was studied in relation to the enzyme content of the pancreatic juice.

The choice of a patient for intubation is important. Any child who has bulky foul stools or diarrhea and who does not respond to the usual treatment should be suspected of having fibrocystic disease of the pancreas until enzyme studies are completed. Occasionally in this condition, the stools are abnormal at birth, but more frequently they do not become bulky and foul until solid foods are added to the diet. Rarely a child is found with this disease whose stools are reported to have been normal since birth (see cases Nos. 21 and 22, Group I). Children who develop a chronic cough without apparent cause, children with bronchiectasis, or children with recurrent bronchitis or pneumonia should also be intubated. The diagnosis of pancreatic fibrosis is often missed when the child comes for treatment of his first attack of pneumonia. When the disease is well advanced, it has often been diagnosed as pertussis due to the striking similarity of the coughs.

Enzyme determinations on duodenal contents are difficult. Many of these difficulties have been pointed out by Davison.[24] Small quantitative deviations from the normal are meaningless. However, if the intubation is done carefully by one who is familiar with the technic of collecting good specimens of juice and if the determinations are carried out by one person trained in the procedures, fairly uniform results may be obtained.

Summary and Conclusions

One hundred and sixty-five children were intubated and the enzyme activity of their duodenal juice studied. Seventy-six patients showed normal potency of all the pancreatic enzymes and had clinical conditions apparently unrelated to pancreatic secretions. The other 89 patients were included in this study and grouped as follows:

Group I: Twenty-three children had minimal pancreatic enzyme activity and presumably were suffering from fibrocystic disease of the pancreas.

Group II: Two children with minimal enzyme activity may have had a pancreatic deficiency of different etiology from that of Group I.

Group III: Four children had transitory partial suppression of trypsin, lipase and amylase. In three, after recovery, repeated studies showed that their enzymes were normal. The fourth child died without the enzyme studies having been repeated. A fifth child had complete suppression of enzyme activity while ill with a respiratory infection. She is included in this group because, coincident with her clinical recovery, there was an appreciable return of enzyme activity. Clinically, these five children had nothing in common.

Group IV (a): Twenty-five children had suppression of lipase activity in conjunction with a normal level for trypsin and amylase. Most of them had some type of gastrointestinal disturbance. Four had diseases of the respiratory system. Sixteen of these children were restudied. The return of lipase activity coincided roughly with a return to health: those who were studied at a time they were clinically well had normal enzyme activity,

while those who were not well still had a reduced secretion of pancreatic lipase. None proved to be early cases of progressive pancreatic deficiency.

Group IV (b): There were no children with deficient trypsin activity in the presence of normal lipase and amylase.

Group IV (c): Sixteen children were deficient in amylolytic activity in conjunction with normal trypsin and lipase. Most of these children had gastrointestinal symptoms. Six of them had celiac disease.

Group V: Eighteen children with extreme malnutrition had normal enzyme activity.

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SPANISH ABSTRACT

Avaluación Clínica del Contenido de Enzima Anormal en el Jugo Pancreático de Niños

Se intubaron 165 niños y se estudió la actividad de enzima de su jugo duodenal. Setenta y cinco pacientes mostraron potencia normal de todos los enzimas pancreáticos y tenían condiciones clínicas aparentemente no relacionadas con las secreciones pancreáticas. Los otros 89 pacientes pueden agruparse como sigue:

Grupo I: Veintitres niños tenían actividad de enzima pancreatico mínima y presumidamente sufrían de enfermedad fibrocística del pancreas.

Grupo II: Pueda ser que dos niños con actividad de enzima mínima hayan tenido deficiencia pancreática de diferente etiología que el grupo I.

Grupo III: Cuatro niños tenían supresión parcial transitoria de tripsina, lipasa y amilasa. En tres, después de la mejoría, repetidos estudios mostraron que sus enzimas estaban normales. El cuarto niño murió sin que se le repitieran los estudios de enzima. Un quinto niño tuvo completa supresión de actividad de enzima cuando estaba enfermo con una infección respiratoria. Se ha incluído ella en este grupo porque hubo una vuelta apreciable de actividad de enzima que coincidió con su mejoría clínica. Clinicamente estos cinco niños no tenían nada en común.

Grupo IV: (a) Veinticinco niños tuvieron supresión de actividad de lipasa en conjunción con una cantidad normal para tripsina y amilasa. La mayor parte de ellos tenían cierto tipo de desorden gastro-intestinal. Cuatro tenían enfermedades del sistema respiratorio. Se volvieron a estudiar 16 de estos niños. El retorno de la actividad de lipasa coincidió grandemente con un regreso a la salud; aquellos que fueron estudiados cuando estaban clinicamente bien tenían actividad de enzima normal, mientras que aquellos que no estaban bien todavía tenían una secreción reducida de lipasa pancreática. Ninguno dió muestra de ser caso temprano de deficiencia pancreática progresiva.

Grupo IV: (b) No hubieron niños con actividad tripsina deficiente en la presencia de lipasa y amilasa normales.

Grupo IV: (c) Diez y seis niños estaban deficientes en actividad amilolítica en conjunción con tripsina y lipasa normales. La mayor parte de estos niños tenían síntomas gastro-intestinales. Seis de ellos tenían enfermedad celíaca.

Grupo V: Dieciocho niños con extrema malnutrición tenían actividad de enzima normal.

616 Medical Arts Building

GLOMERULAR FILTRATION RATE IN CHILDREN WITH SICKLE CELL DISEASE

By PHILIP L. CALCAGNO, M.D., JOHN MCLAVY, B.S., AND THOMAS KELLEY, M.D.
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STUDIES of kidney function in sickle cell anemia have not been previously reported. Diggs[1] considered the degenerative and proliferative changes in kidneys to be a constant feature of long standing severe cases of sickle cell anemia. Engorgement with disfigured red blood corpuscles was encountered in the distended capillaries of the kidneys in patients with sickle cell disease.[2] Yater[3] found sclerosis of the glomeruli in the kidney on routine necropsy reports. It seemed reasonable that a study of the functioning kidney might reveal information which would not consistently appear at pathologic examination.

CLINICAL MATERIAL AND METHODS

Sodium thiosulfate was used to determine the rate of glomerular filtration as described by Newman et al.[4] The patients were fasting in the basal state. Collections of specimens of blood and urine for blank determinations were made before injection of sodium thiosulfate. A 6% sodium thiosulfate solution was injected within 10 to 15 min. The dosage was from 0.3 to 1.0 gm./4.5 kg. body weight. Fifteen minutes were allowed for equilibration throughout body fluids. Blood samples were taken from the arm opposite the one into which the injection had been made. Urine was collected from the bladder by a catheter and the bladder was washed out with 10 to 20 cc. of sterile water.

The diagnosis of sickle cell anemia was made when 95 to 100% sickling was observed in smears from the peripheral blood associated with abnormally high reticulocyte and leucocyte counts. Only patients with hemoglobin levels below 50% and those who had not received previous transfusions, except for Patient 8, were accepted for the study.

Clearances were measured on patients with the following disorders: 5 patients with sickle cell anemia, 2 patients with the sickle cell trait and 1 patient with chronic anemia secondary to uncinariasis.

RESULTS

Results are shown in Table I which presents all the pertinent data. Five patients with sickle cell anemia presented below average glomerular filtration rates. All values were corrected to 1.73 sq. m. of body surface area. Two patients who exhibited the sickle cell trait only showed a normal glomerular filtration rate.

Patient 8, who was said to have a chronic anemia secondary to uncinariasis for 1 yr., showed normal glomerular filtration. Since this patient received 2 transfusions prior to the measurement of the glomerular filtration rate, the significance of this rate was not fully understood.

DISCUSSION

It has been shown that a renal functional abnormality develops in chronic sickle cell anemia. There may be several possible explanations regarding the pathogenesis for the low filtration rates in these patients.

Bradley[5] was impressed with the afferent arteriolar vasoconstriction in patients with chronic anemia which was indicated after finding low filtration fractions and a larger reduction in renal blood flows. Whether reduced renal blood flow occurs in sickle cell

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This investigation was accomplished by the authors while on duty with the Army of the United States in the Canal Zone.

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TABLE I

Subject	Wt. kg.	Age	Sex	Hgb. gm.	Body surface sq. m.	Periods	Glomerular filtration ml./min./1.73 sq. m.	Diagnosis
1. R.L.	29.6	9	M	6.8	1.89	6	74.3	Sickle cell anemia
2. L.N.	13.6	4	F	7.0	0.612	3	50.7	" " "
3. D.U.	21.3	9	M	6.5	0.871	3	69.6	" " "
4. L.F.	41.3	15	M	7.2	1.370	3	94.0	" " "
5. H.C.	22.7	12	F	7.0	0.890	3	70.6	" " "
6. G.S.	25.0	7	M	13.4	0.958	3	120.7	Sickle trait
7. E.J.	15.4	6	F	14.0	0.672	2	150.0	" "
8. G.DeL.	54.5	19	M	5.9	1.620	3	144.5	Anemia secondary to uncinariasis

Mean value glomerular filtration rate.....131 ml./min./1.73 sq. m.
Normal male above 2 yrs.
Mean value glomerular filtration rate.....117 ml./min./1.73 sq. m.
Normal female above 2 yrs.
Glomerular filtration rate.....45–120/1.73 sq. m.
Range under 2 yrs.

anemia with a concomitant fall in filtration fraction will not be known until further studies are accomplished. Circulatory stasis in the small vessels of internal organs, muscle and other tissue has been demonstrated in patients with sickle cell traits;[6] yet two patients with the sickle cell trait revealed a normal glomerular filtration rate. One would presume the striking difference in the patients with sickle cell disease as compared to the patients with the sickle cell trait may be due to the severe chronic anemia.

Congestive heart failure and shock[7] were not present in these cases. Consequently, these factors could not be used to explain the lowered glomerular filtration rate.

Summary

Renal function has been studied quantitatively in five patients with sickle cell anemia, all of whom were proved to have reduced glomerular filtration rates. Two patients with sickle cell trait revealed normal glomerular filtration rates. Possible mechanisms responsible for reduced glomerular filtration flows are discussed.

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SPANISH ABSTRACT

Proporción de Filtración Glomerular en Niños con Enfermedad Hematié Falciforme

Se ha estudiado la función renal cuantitativamente en 5 acientes con anemia hematié falciforme, de los cuales todos demostraron tener proporciones de filtración glomerular reducidas. Dos pacientes con características de hematié falciforme revelaron proporciones de filtración glomerular normales. Se tratan los mecanismos que pueden ser responsables por las corrientes de filtración glomerular reducidas.

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GROWTH PATTERN OF PREMATURELY BORN INFANTS

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THE STUDY of normal growth in weight, length, sitting height and head circumference of normal prematurely born babies as observed in a series of about 500 premature infants was undertaken at the Cook County Children's Hospital Premature Station and Out-Patient Department.

Although growth charts, graphs, grids and tables for growth patterns of prematurely born infants have been published by other investigators, they are in many instances difficult to use for comparative evaluation of individual cases or even of larger groups because of several shortcomings concerning the composition of the groups observed and their statistical evaluation. These difficulties have been taken into account by breaking the present group into smaller categories of more uniform character for analysis, thus facilitating the use of these data for comparison by future investigators or practising physicians concerned with the management of premature infants.

MATERIAL AND METHODS

The infants were observed during a 2 yr. period (1945-1947); they were seen at 2 wk. intervals; roentgenograms were taken every month and calcium, phosphorus and phosphatase determinations of the blood were made at least once on every patient during his period of observation. Different vitamin D preparations and dosages were administered. No differentiating influence upon the growth of the children was observed by the various preparations and dosages of vitamin D used.[1] We therefore felt justified in utilizing the data recorded on these infants for observation of the normal growth of premature infants.

The selection of premature babies was made on the basis of birth weight. Babies with a birth weight below 2268 gm. were considered premature and admitted to the premature nursery. No attempt was made to determine the actual time of gestation; the rather arbitrary weight limit as indication for need of premature care is found practical in the management of large numbers of infants, but permits errors by including small full term babies or excluding large premature infants from the series. After the infants reached a weight of 2268 gm. or slightly above, they were discharged to the special outpatient department for premature infants. The actual chronologic age of the infants as determined by the date of birth was recorded and no consideration given to a possible correction with regard to the child's conceptional age and premature birth. Such a correction would have to be based mainly on a history of menstruation and signs of pregnancy of the mother and would be subject to too many sources of error and was therefore not attempted.

Most babies came from the lower economic group of the population. Out of a total of 500 babies only 163 were used for this study. All babies studied here were observed for a total of 8 mos.; thus, all who died before reaching this age and those who were not brought back by their mothers for regular 2 wk. check-ups were eliminated. A small number who fell seriously ill during the observation period and were markedly retarded in some phase of their growth were also omitted. This left the 163 babies, observed at 2 wk. intervals for a period of 8 mos. Of these, 138 (84.7%) were Negro and 25 (15.3%) white children.

Since the growth pattern of the Negro population is reported to be somewhat different from that

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of the white population (Woodbury[2]),* a statistical evaluation of the group, if considered *in toto*, would be influenced materially by its Negro fraction and would therefore be neither a true "average" of the population nor a standard with which to compare children of either race separately. Therefore the data were also analyzed in subdivisions by color.

Further subdivisions were made into groups of different birth weights. Since there are discrepancies in the growth curves of patients of different birth weights, it was necessary to make these separations in order to compare the findings with publications by other authors and to facilitate future observations and comparisons of groups or individual infants.

Subgrouping by sex was necessary because of the well known observation that even during this early age period babies of different sexes grow at different rates.

The observation period of 8 mos. was subdivided into 2 mo. periods because an uneven, yet definitely patterned growth process was observed in practically all babies during this period and only a subdivision of the observation span permitted the demonstration of these growth patterns; calculation of the data over an undivided 8 mo. period would fail to demonstrate the variations occurring characteristically during this time span. If the growth process of a baby aged 4 mos. is to be checked it must be compared with data obtained from infants of this same age level (4 mos.) as it would be inaccurate to compare its growth with an "average growth rate" as obtained over a period of 8 mos. or any other age period. This subgrouping into 2 mo. intervals also permits comparison with data found by other authors who used observation periods other than 8 months.

Discussion

Weight Gain: Growth as measured by weight gain does not proceed on an even scale. In the present group, maximal gain occurred during the second and third two month period (Table I, Chart 1).

In this discussion of "normal growth," reference must be made to the feeding method employed, as different methods could have produced somewhat different results. The milk formula at the hospital consisted of either a dilution of evaporated milk or whole cow's milk modified by the action of pancreatic proteolytic enzyme (enzylac®). Upon discharge, all babies were given an evaporated milk, water and corn syrup feeding mixture. At about 3 months of age cereals, at 4 months vegetables, at 5 months fruit and at 6 months egg yolk were added to the diet. After 6 months, it was left up to the mother to add custards, puddings, soups, meat, etc. Vitamin D was added from the first days of life. Vitamin C was supplied in form of 50 mg. ascorbic acid tablets daily while in the hospital and in the form of orange juice after discharge from the hospital. Milk and vitamins were dispensed free of charge to all mothers, thus eliminating the influence of economic differences upon the growth of children with regard to this part of nutrition. During the latter part of the eight month observation period when additional foods—which the mother had to supply—became of more importance the financial situation of the parents may have influenced the growth of the children to some degree. This may be an explanation for the lagging behind of the Negro children as compared to the white group during the last two 2 month periods.

As to the amount of feeding, the hospital stay and the home-care period must be considered separately. Whereas liberal feeding on a semi-self demand schedule[3] was permitted after discharge from the hospital, the diet during the hospital stay (averaging

* Woodbury's data were selected because of their comprehensive character and because they are broken down by monthly age periods and by race. His children are full term infants, which offers the opportunity to compare the growth of prematures with full term babies. Comparison of our figures with those of other investigators of premature growth meets with difficulties as discussed in the following pages.

about six weeks) was rigidly controlled, and was probably calorically below the amount which most of these babies would have been able to take, as demonstrated by the rapid increase of food intake after discharge from the hospital, according to the "demands" of

TABLE I

AVERAGE DAILY WEIGHT GAIN BY BIRTH WEIGHT GROUPS (GM.)

Group	No. of pts.	0–2 mos.	2–4 mos.	4–6 mos.	6–8 mos.	0–8 mos.
Group 1 under 1000 gm.	4	11.0	19.9	26.5	20.3	19.4
Group 2 1000–1500 gm.	16	10.5	23.5	26.5	19.8	20.1
Group 3 1500–2000 gm.	94	14.5	29.4	25.0	17.2	21.5
Group 4 over 2000 gm.	49	14.8	30.0	24.7	17.0	21.6
Total	163	14.2	28.6	25.1	17.4	21.3

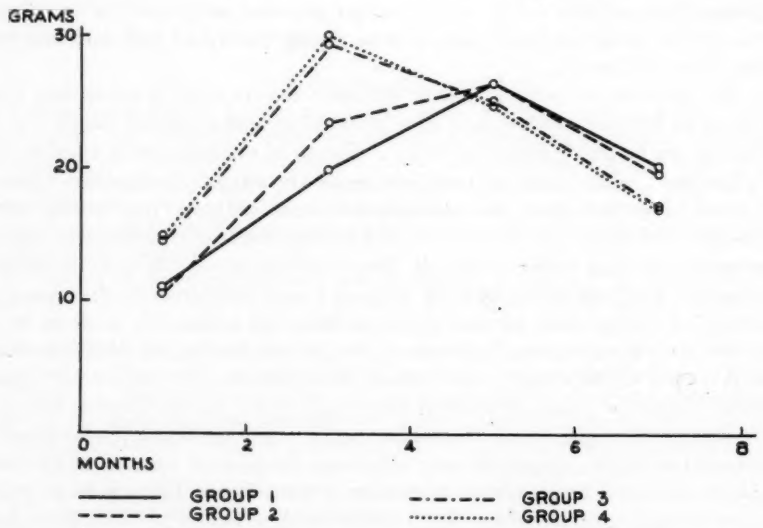

CHART 1. Average daily wt. gain in 2 mo. periods arranged by birth wt. groups.

the child. Because of this restricted diet, maximal gain in weight was probably not obtained during the hospital stay. Although a more rapid gain in weight would have led to an earlier discharge from the hospital, it is doubtful whether the respiratory and temperature regulating apparatus and defense mechanism against infection of these young infants would be ready to endure earlier exposure to life outside the premature station. Furthermore, it is felt that a higher caloric intake may be a dangerous undertaking since the labile tolerance of the intestinal tract of premature babies makes them susceptible to diarrhea, and "overfeeding" is one of its causes. The danger of diarrhea from any cause

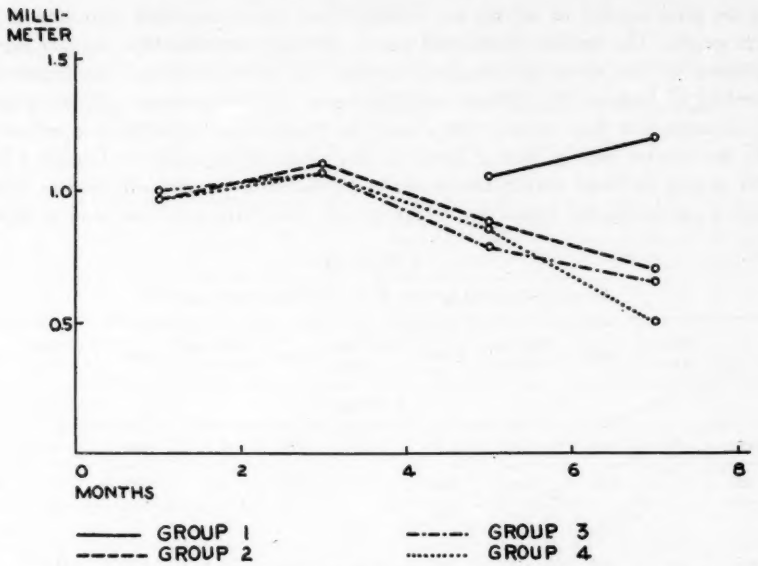

CHART 2. Average daily length gain in 2 mo. periods arranged by birth wt. groups.

TABLE II

AVERAGE DAILY LENGTH GAIN BY BIRTH WEIGHT GROUPS (MM.)

Group	No. of pts.	0–2 mos.	2–4 mos.	4–6 mos.	6–8 mos.	0–8 mos.
Group 1 under 1000 gm.	3	—	—	1.05	1.2	—
Group 2 1000–1500 gm.	15	0.97	1.1	0.88	0.7	0.91
Group 3 1500–2000 gm.	95	1.0	1.07	0.78	0.65	0.875
Group 4 over 2000 gm.	49	0.97	1.07	0.85	0.5	0.846
Total	162	1.0	1.03	0.82	0.62	0.867

Note: Accurate length measures of the smallest group were not obtained at birth. Because of missing length measures in 1 baby of each of the 1st 2 groups and the addition of 1 infant to the 3rd wt. group, the total number of babies is 1 less than in Table I.

in infants, and particularly in premature infants, is well known.

Length Gain: Table II and Chart 2 demonstrate the gain in length, again considering the total group (both races and sexes). It runs a less pronounced yet very similar course as the weight table, showing the peak of growth of the entire group in the second two month period.

Growth Pattern of Different Birth Weight Groups: In observing the weight gain of babies of various birth weights, considerable variations are observed. To demonstrate this

fact the total number of infants was broken down into four groups according to their birth weight. The smaller infants did not in all cases constitute the younger ones, as explained by the previously mentioned method of selection of the "premature baby" according to birth weight without consideration of true intrauterine (postconceptional) age. It seems that these infants with a lower birth weight get a later start in weight gain than the heavier ones as seen in Chart 1. The peaks of the curves of Groups 1 and 2 occur during the third two month period as compared to the peaks of Groups 3 and 4 which occur during the second two month period. This "late start" may find its explana-

TABLE III

AVERAGE GROWTH OF OUR BOYS AND GIRLS (GM. AND MM.)

	No. of pts.	Birth	Daily gain 0–2 mos.	2 mos.	Daily gain 2–4 mos.	4 mos.	Daily gain 4–6 mos.	6 mos.	Daily gain 6–8 mos.	8 mos.
A. Weight										
Boys	66	1852	15.0	2756	29.5	4525	26.0	6082	17.0	7103
Girls	97	1810	13.6	2628	28.1	4312	24.5	5785	17.7	6849
B. Length										
Boys	66	433	1.02	494	1.07	558	0.83	608	0.65	647
Girls	94	434	0.98	493	1.0	553	0.82	602	0.6	638

tion in the longer hospital stay with a strictly controlled relatively low caloric diet of the smaller babies, or may be due to the greater birth trauma to these small babies or due to their lower postconceptional age and shorter intrauterine life. These groups of smaller babies show a greater daily weight gain during the last (fourth) two month period as if they were making an attempt to catch up with their bigger brothers. The initially slow gain in weight of the smaller group influences its progress to such an extent, however, that it shows a lagging behind in average daily weight gain if the total period from birth to 8 months is considered (Table I). The "total average" is influenced strongly by the large number of infants in Groups 3 and 4.

A pattern somewhat similar to the weight curves is shown by the course of the length curves. However, neither birth shock nor food intake should influence the growth in length to any great degree and in fact the differences observed in the weight gain during the second and third two month periods between the smaller and larger babies cannot be observed in the length studies. Here too, however, the infants of the lower birth weight groups (Groups 1 and 2) average higher figures in daily length increase during the last (fourth) two month period than the infants of higher birth weight groups (Table II, Chart 2). Again we might attribute this retardation to the "shock" of birth which might exhibit its effect more profoundly in direct ratio to the degree of immaturity of the particular infant in question.

Growth Pattern of Boys and Girls: In comparing the growth pattern of all boys with that of all girls, we find the birth weight and length of boys and girls were about the same but the boys were somewhat heavier and taller at 8 months of age; the difference, however, was not marked. This same pattern is expressed in their daily weight and length

TABLE IV

COMPARISON OF WEIGHT—WHITE BOYS AND GIRLS (GM.)

	No. of pts.	Birth	Daily gain 0–2 mos.	2 mos.	Daily gain 2–4 mos.	4 mos.	Daily gain 4–6 mos.	6 mos.	Daily gain 6–8 mos.	8 mos.
Our boys	9	1947	14.1	2791	30.5	4619	26.6	6215	20.1	7420
Our girls	16	1850	14.7	2730	31.3	4609	29.0	6349	21.9	7662
Woodbury boys				5350	22.3	6690	17.0	7710	12.8	8480
Woodbury girls				4980	20.3	6200	16.2	7170	12.5	7920

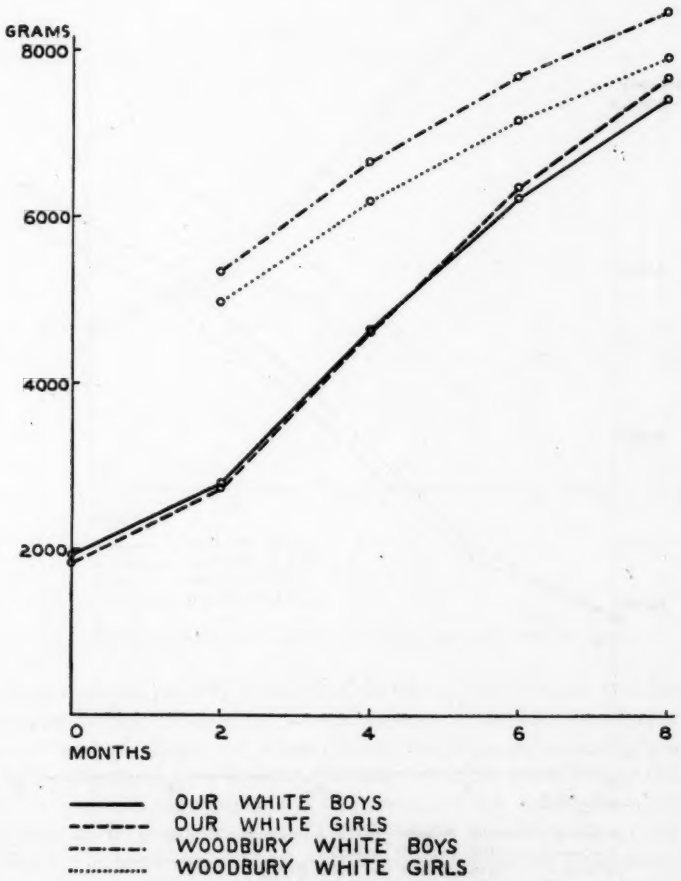

CHART 3. Comparison in wt.—white boys and girls.

TABLE V

COMPARISON OF WEIGHT—NEGRO BOYS AND GIRLS (GM.)

	No. of pts.	Birth	Daily gain 0–2 mos.	No. of pts.	2 mos.	Daily gain 2–4 mos.	No. of pts.	4 mos.	Daily gain 4–6 mos.	No. of pts.	6 mos.	Daily gain 6–8 mos.	No. of pts.	8 mos.
Our boys	57	1837	15.2	56	2750	29.3	57	4510	25.8	57	6061	16.6	55	7057
Our girls	81	1802	13.4	80	2609	27.4	81	4254	23.7	81	5674	17.0	80	6696
Woodbury boys				71	4531	25.25	76	6046	18.75	56	7171	10.4	63	7793
Woodbury girls				71	4146	25.25	92	5661	14.0	65	6500	12.17	65	7230

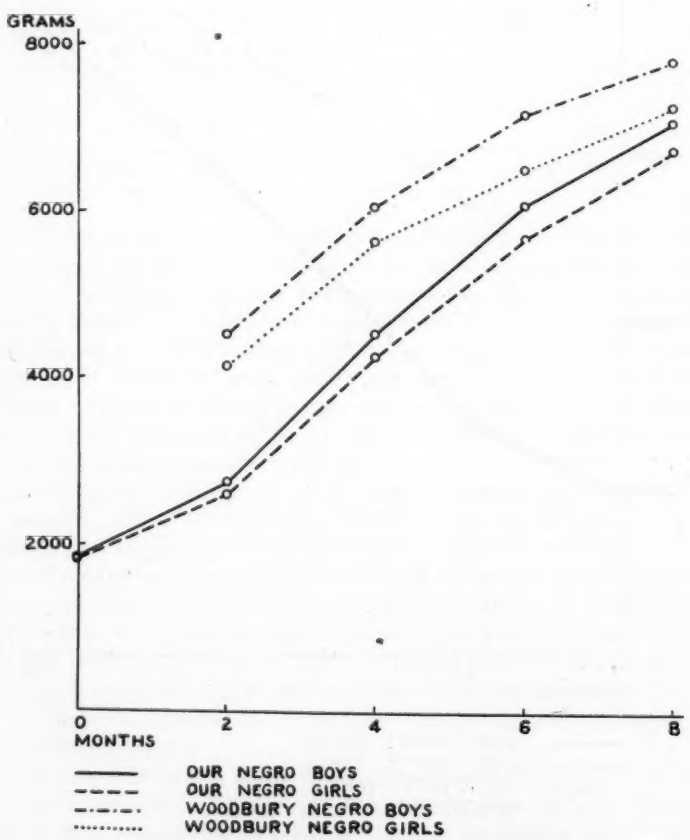

CHART 4. Comparison in wt.—Negro boys and girls.

gain, broken down into two month periods, with the exception of the fourth two month period in the weight chart, where the girls slightly surpass the boys (Table III).

The white girls, although lighter in weight at birth than the white boys, surpass them at the age of 8 months (Table IV, Chart 3). This, however, seems to be statistically insignificant because a comparison with the Negro group and the findings of other authors

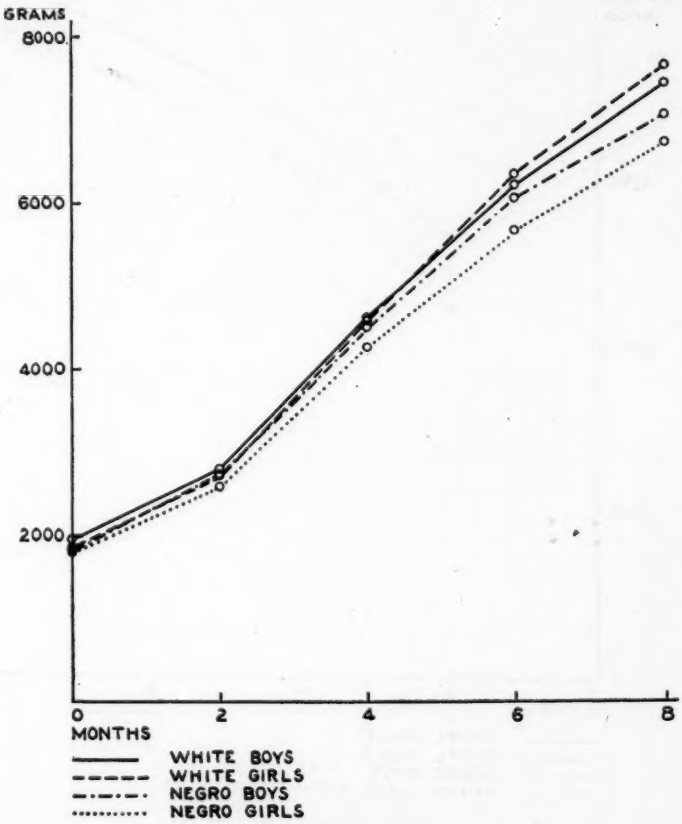

CHART 5. Comparison in wt.—our Negro and white boys and girls.

show the persistent superiority in weight of the boys (Table V, Chart 4). The discrepancy can probably be best explained by the small number of white children in this series.

Growth Pattern of Negro and White Infants: The Negro infants had approximately the same birth weight and grew at about the same rate as the white infants (Chart 5). All infants received milk and vitamins free from the clinic, thus making the nutritional status independent of the economic situation of the parents, at least during the first months of life. This fact is borne out in Chart 5 which shows the growth curve during the first 4 months of life to be almost equal to that of the white children. The slight lagging behind in growth of the Negro children during the third and fourth two month periods was

probably influenced by the economic situation of this group, which has to be taken into account at this age when supplementary foods such as cereal and vegetables, which were not supplied gratuitously by the clinic, constituted an essential part of the caloric intake. It must also be taken into account that the patients were children of mothers who were

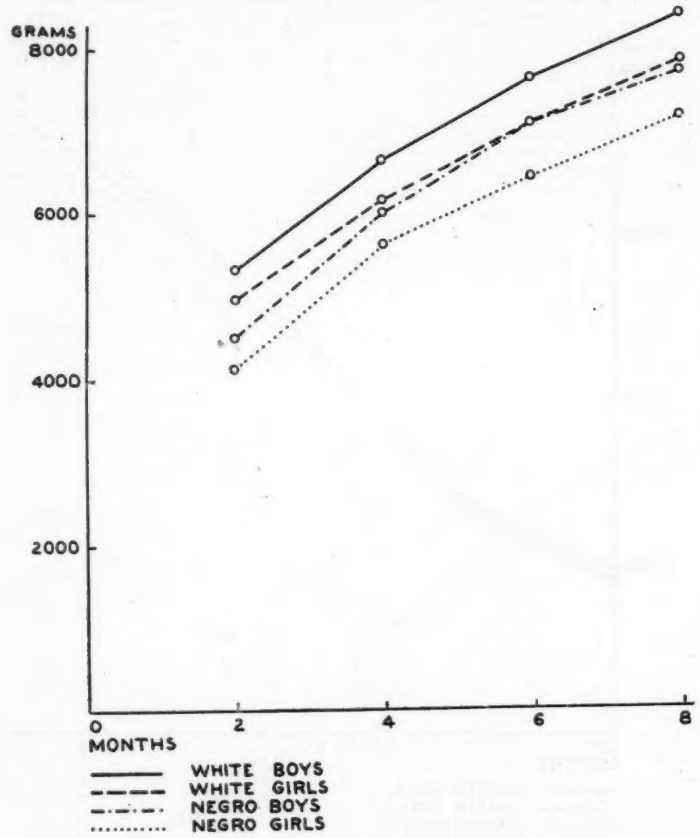

CHART 6. Comparison in wt.—Woodbury's Negro and white boys and girls.

willing to cooperate and to attend the clinic regularly; those who did not show this interest were dropped from the study. A less strictly controlled group might have altered the findings somewhat.

On Woodbury's tables a definite difference in the two racial groups can be noted (Chart 6), but this discrepancy may find its explanation in the fact that Woodbury drew his information from the Negro population at large, thus basing his findings most likely on an economically underprivileged part of the total population. His total number of Negro children is also much smaller than that of his white children and his tabulating methods differ in the two racial groups. Whereas he tabulates the white children by exact

age, his Negro children are tabulated in scores (e.g., children 1 month, under 2 months). This, too, produces a certain inaccuracy.

An attempt was made to statistically compare Hess' figures[4] with ours, but several difficulties were encountered: 1. Hess uses the chronologic age corrected for prematurity, whereas we use the true uncorrected age. 2. Hess' series consists of less than 20% Negro

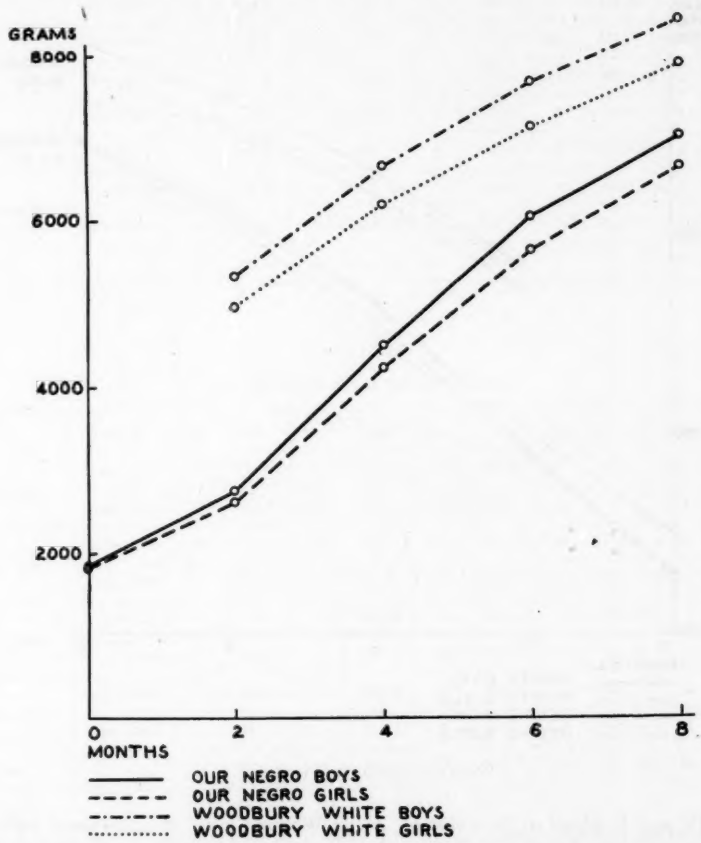

CHART 7. Comparison in wt.—Woodbury's white with our Negro boys and girls.

children which are not separated in his growth analysis, while our series consists of more than 80% Negro children and, in view of some differences in the growth processes of the two races, a statistical comparison would be incorrect. 3. Hess does not subdivide his group into babies with different birth weights except for one series of tables where he considers babies with a birth weight above 2000 gm. and those below 1500 gm., omitting data on the largest group, the one with a birth weight between 1500 and 2000 gm. This is the most important group, not only because of its numerical superiority, but also because it constitutes the group of babies most likely to survive, and yet small enough to present the real problems of prematurity.

To get a truer picture of the actual growth of our infants, it would be more accurate to compare our largest group, the Negro infants, with Woodbury's largest group, his white children. Chart 7 demonstrates this graphically and shows that the curves approximate each other at the eight month level, thus giving evidence of the fact that premature babies grow faster than full term infants. This can be seen with greater accuracy on

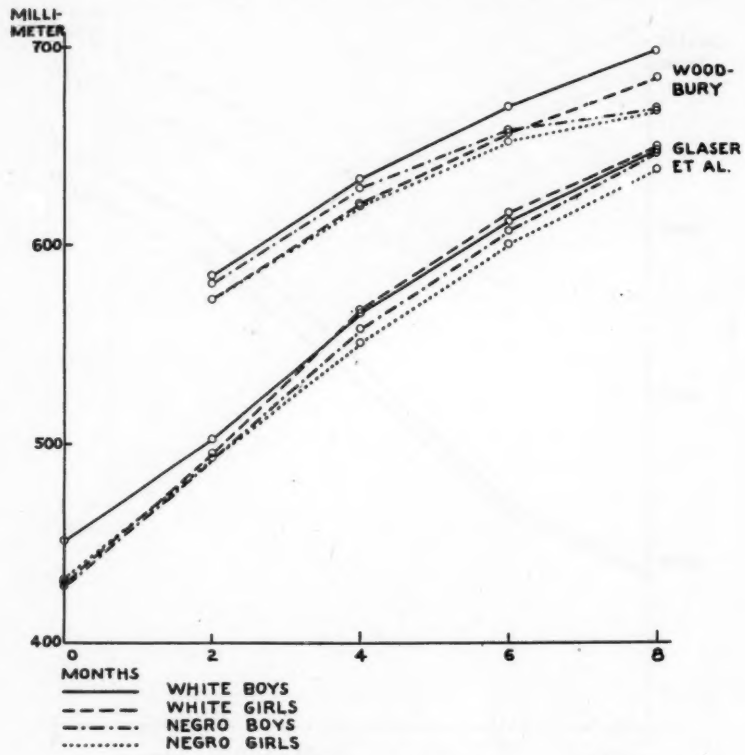

CHART 8. Comparison in length.

Tables IV and V where in the column, "Daily Weight Gain," the premature babies are always considerably ahead in weight growth of the full term infants of Woodbury. Attention should be drawn to the fact that Woodbury's figures were published in 1921. The improved feeding technics of the last years would probably change the full term growth pattern.

If the length is considered rather than the weight, a similar picture arising from a comparison of the growth pattern in boys and girls, Negroes and whites, is found. Chart 8 gives a graphic comparison of the four groups and demonstrates that the girls and boys increase their length at a similar rate, our Negro girls (representing the larger and therefore more accurate group) lagging slightly behind the boys, as is the case in full term infants of Woodbury. In our smaller group of white children, a slight acceleration of the length growth of the girls over that of the boys, similar to their pattern on the weight

TABLE VI

AVERAGE SITTING HEIGHT (MM.)

	Birth wt.	No.	2 wks.	No.	2 mos.	No.	4 mos.	No.	6 mos.	No.	8 mos.
Negro boys	1500–2000	13	304.8	21	341.6	28	381.0	34	420.9	34	453.4
	over 2000	3	313.2	7	337.8	13	386.1	15	414.8	15	442.0
Negro girls	1500–2000	8	312.4	24	331.2	33	378.5	34	415.3	35	448.8
	over 2000	4	317.5	12	339.8	20	373.4	22	409.4	23	439.2
White boys	1500–2000	0	—	1	368.3	3	370.3	5	401.3	4	429.3
	over 2000	1	330.2	3	342.9	5	381.0	4	425.45	4	462.0
White girls	1500–2000	4	311.15	6	342.9	7	399.0	8	430.3	7	453.6
	over 2000	0	—	4	349.25	5	388.6	5	436.9	6	447.8
Total		33	310.64	78	338.58	114	380.75	127	417.32	128	447.55

TABLE VII

AVERAGE HEAD CIRCUMFERENCE (MM.)

	Birth wt.	No.	2 wks.	No.	2 mos.	No.	4 mos.	No.	6 mos.	No.	8 mos.
Negro boys	1500-2000	15	311.9	31	350.3	37	383.5	37	415.0	36	438.9
	over 2000	3	313.2	13	352.0	15	395.7	15	421.1	15	437.4
Negro girls	1500–2000	8	315.0	33	346.7	40	380.0	37	410.2	37	432.6
	over 2000	5	317.5	23	353.6	26	385.3	25	411.7	26	432.1
White boys	1500–2000	0	—	3	342.9	6	386.3	6	418.1	5	430.5
	over 2000	1	330.2	4	360.4	5	401.3	4	421.6	4	441.2
White girls	1500–2000	4	317.5	7	346.4	8	391.4	8	414.0	7	431.8
	over 2000	1	317.5	6	358.1	6	394.7	6	429.3	6	442.0
Total		37	314.71	120	350.52	143	385.57	138	414.78	136	435.36

tables, is observed. Woodbury's normals show throughout a somewhat superior length of the boys as compared to the girls. The length development of the Negro children lags somewhat behind that of the white children, a pattern similar to the one observed on the weight tables. Whether this finding is conditioned by racial-constitutional differences or due to economic-nutritional differences between these two groups remains to be established. It is, however, remarkable that the differences, if expressed in percentages, are much less noticeable for the skeletal growth than for the weights (weight of Negroes at 8 months 9.7% below weight of white children, length of Negroes 1.25% below length of whites). If nutritional factors were the cause of the weight-length growth discrepancies one would expect them to be reflected to a much greater degree in the weight growth than in skeletal growth.

Head Circumference and Sitting Height: Measurements of the largest circumference of the head and of the sitting height were taken on the infants. These measurements were not taken with the same consistency as the weight and length measurements due to the technical difficulties in a busy clinic. Therefore the total number of measurements available is not as high as the data for length and weight. The nature of these measurements also permits certain inaccuracies which were greater than those in weight and length.

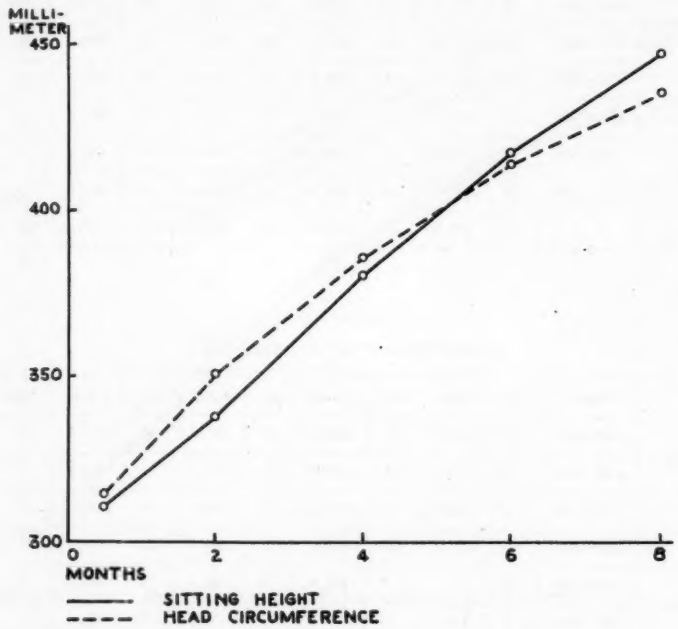

CHART 9. Comparison of average sitting ht. and head circumferences.

Nevertheless, it was found significant enough to compile these data and to draw certain conclusions from the figures. The data were again compiled at two month intervals. The first measurement was taken at the age of 2 weeks and not at birth as for the other data (Tables VI and VII, Chart 9).

The measurements for head circumference and sitting height were almost equal at the same age levels. The rate of growth of these two factors is therefore similar up to the age of 8 months, with a slight acceleration of the sitting height as compared with the head circumference beginning with the third two month period (Chart 9). This relative acceleration can be expected to increase proportionately with the age of the child.

There seems to be no significant difference between the two races or between the babies of the lower and higher birth weight groups, as the variations fall within the realm of statistical errors.

Considering the two largest groups, the Negro boys and girls, it seems that, beginning at 4 months, the data for the boys are somewhat higher than those for the girls. Although

the differences are so small as to fall within the standard deviation, they occur with consistency and correspond to the findings for the total length and weight and therefore permit the conclusion that head circumference and sitting height of the boys are larger than those of the girls. The measurements for the first two weeks of life are too few in number and suffer inaccuracies because they were usually taken quickly and without removing the infant from the incubator and can therefore not be regarded as valid.

The increase in sitting height during the individual two month periods seems to be greatest during the second and third periods (Chart 9), an observation similar to that noted in the total growth in length and weight. The growth of the head circumference shows a progressive, although small, amount of slowing down during these eight months of observation, a trend which is known to prevail to a much more marked degree later on.

The close approximation of the two measurements for the entire eight month period of observation emphasizes again the practical importance of the use of these comparative measurements. Pirquet[5] in 1916 pointed out the value of the measurement of the sitting height by describing the constant relationship between this measure and the body weight.

Whereas the type of statistical evaluation as done in this study permits a comparison of the infants with each other and with data obtained from other studies, Wetzel's method of investigation permits an evaluation of the child's progress according to his own body structure. Such a study has been done and will be published separately.

Summary

One hundred sixty-three prematurely born infants were observed from birth to 8 months of age. Their growth progress was recorded at regular intervals and evaluated in detail as to the pattern of the weight, length, head circumference and sitting height increment. Variations conditioned by differences in race, sex and birthweight were analysed. A comparison of these premature infants with normal full term infants was made. The data were evaluated statistically and graphically.

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Spanish Abstract

Patrón de Desarrollo de los Infantes que Nacen Prematuramente

Ciento sesenta y tres niños que nacieron prematuramente fueron observados durante los primeros 8 meses de su vida y se estudió el patrón de desarrollo. El aumento máximo diario de peso y largo ocurrió del segundo al sexto mes de vida. Este máximo diario ocurrió más tarde en niños más pequeños. El desarrollo del largo siguió un curso similar pero menos pronunciado. Los varones excedieron a las hembras en peso y largo a los 8 meses de edad. Los niños negros y blancos crecieron a una misma proporción, solo que los negros pesaban un poco menos al principio del cuarto al sexto

mes. Se encontró que el crecimiento de la circunferencia de la cabeza y la altura sentados estaban parelelos, con una ligera deceleración en el crecimiento de la cabeza durante la segunda parte del período de observación. Se trata la posible influencia del manejo dietético de los niños y se presentan descubrimientos en forma de tablas y cuadros.

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Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S COLUMN

The President and the Executive Board send their greetings to the membership of the Academy of Pediatrics for the new year.

This column will appear irregularly from time to time in an effort to keep the membership apprised of developments which affect the Academy and which must be considered by the Executive Board. The President and the District Chairmen are elective officers of the Academy and in the true sense of democratic representation can only attempt to interpret the opinions of the membership in their action on problems which arise. American medicine is now confronted with many problems upon which neither the individual nor the organization can avoid taking a position. The action of your executive officers must be predicated upon the expression of opinion by the membership. It is hoped that you will keep your officers informed of individual and group opinions upon controversial issues in order to guide their action. The columns of PEDIATRICS are open to the membership in "The Pediatrician and the Public" but it is most desirable that you communicate with your officers directly for their information.

The San Francisco session was astonishingly well attended considering the handicap which distance imposed upon many of the members. I should be remiss in not expressing the pleasure of the local Fellows that so many should have come so far and contributed so much. Dr. Edgar E. Martmer and his Program Committee are to be congratulated not only because of the excellence of the program but also because they were able to effect last minute substitutions for participants who, because of illness, were unable to attend, without impairing the structure of the meeting. The contributions of the various discussants and of the leaders of seminar, panel and round table sessions and the support of the National Foundation for Infantile Paralysis should be gratefully acknowledged. Nor should one fail to note the numerous contributions to the meeting and to the entertainment of the members made by many commercial firms whose interest in the Academy somewhat transcends a purely business relationship.

Individual papers presented at this session occupied a prominent part of the program. The discussions presented by the winners of the Borden and Mead Johnson awards contributed greatly to the scientific excellence of the program. It is earnestly hoped that future meetings should be the sounding board for the most important contributions in the advance of pediatrics.

A summary of the action of the Executive Board and of the business session will shortly be presented to the membership. The report of the Committee on Reorganization was presented for discussion by Drs. Borden S. Veeder and James M. Baty. Final action on this report was deferred for a mail vote of the membership to whom it will be sent. It is desired that in this vote the members will not only express their approval or disapproval but add their personal comments.

This Committee recommends a change in the over-all direction of Academy affairs to embrace our

relationship to the problems of child health and to other organizations concerned with this problem together with the operation of purely intra-Academy management. Extramural activities such as those of the ICH Committee would thus be brought under central direction completely responsible to the Academy together with the various aspects of business administration. The approaching retirement of Dr. Clifford G. Grulee makes it imperative that some plan of future direction be worked out.

The Committee for Improvement of Child Health presented its program for eventual absorption into the central workings of the Academy so that the direction of Academy activities would be completely centralized. It was the general feeling that abrupt cessation of the activities of the ICH Committee was unthinkable. The Executive Board agreed to subsidize this Committee to the extent of the Director's salary for a period ending at the next annual meeting, to fill out this interim period. The appointment of Dr. Warren R. Sisson as chairman of this Committee will insure the final integration of its activities with those of the Academy as a whole.

A preliminary interpretive report of this committee has been distributed to state chairmen for discussion before its final release in completed form. It is to be hoped that as many of the members as possible will see and comment on this report before its completion.

Dr. James G. Hughes reported his contact with the American Legion with respect to their objectives for child health activities. His report sets a pattern for Academy action in many fields: cooperation on a national scope with all organizations which have a common interest in matters which are the concern of the Academy. Of great importance, however, is his concept that the Fellows of the Academy should place themselves at the disposal of such agencies in carrying out local community enterprises. The attainment of many of the objectives of the Academy will best be served not only through planning of national scope but by the earnest efforts of an alert and interested membership working on community activities.

January 14 is the birthday of Clifford G. Grulee. I know that I bespeak the feeling of the entire membership in conveying to him an expression of warm personal affection on the part of every member of the Academy.

EDWARD B. SHAW, M.D.
President

Round Table Discussion

CERTAIN ELECTROLYTE DISTURBANCES IN RENAL INSUFFICIENCY

ELVIRA GOETTSCH, M.D., *Chairman,* Los Angeles, Calif.; RICHARD W. LIPPMAN, M.D., Los Angeles, Calif.; JOHN A. LUETSCHER, JR., M.D., San Francisco, Calif.

TALCOTT BATES, M.D., Monterey, Calif., and M. G. PETERMAN, M.D., Milwaukee, Wis., *Secretaries*

Chairman Goettsch: The word "uremia" was coined by Piorry in 1840 and literally means "retention of urine in the blood." Uremia was thought to be an intoxication due to accumulation in the blood of waste products which the kidneys could not excrete. The increase in plasma urea N was at first considered the cause of the toxicity and later retention of aromatic substances was incriminated. Recently elevation of the plasma inorganic phosphate (HPO_4) and sulfate (SO_4) was appreciated. Retention of the end products of protein metabolism occurs in the plasma when renal function is impaired; even if no food is consumed, catabolism of body tissue cells results in the accumulation of these substances.

The word "azotemia" was originally coined to designate the clinical syndrome resulting from the retention of nitrogenous waste products, but currently it connotes rather abnormal elevation of blood NPN only. In uremia, azotemia is attributed to a decrease of functioning glomeruli. Elevation of the blood NPN without intrinsic renal disease is usually called prerenal or extrarenal azotemia, and is seen if excessively high protein diets are consumed, with decreased renal blood flow as in cardiac decompensation, or with marked reduction in the rate of urine flow associated with dehydration. In diarrhea with excessive loss of base and H_2O through the stools, intracellular H_2O moves into the extracellular compartment. Even though the kidney excretes concentrated urine, the plasma volume cannot be maintained and peripheral circulatory failure results.

By 1912 prerenal azotemia in dehydration and shock was differentiated from renal azotemia and it was recognized that reduced circulation of blood through the kidney was the primary cause rather than intrinsic renal disease.

The realization finally came that retained urinary constituents in the plasma may cause secondary changes which produce deleterious results. The retention of HPO_4 in the plasma of itself was not toxic; but HPO_4 retention caused depression of the Ca level which in turn set in motion complex reactions affecting the parathyroid glands which led eventually to severe bony abnormalities.

Renal insufficiency may be heralded by disturbances in the acid-base balance as in diabetes; retention of fixed acid in the blood depresses the plasma $H.HCO_3$ and, when the buffer capacity is exceeded, eventually lowering pH concentration results. Intrinsic renal disease may interfere with the production of ammonia by the kidneys, which permits the loss of fixed base from the body with subsequent production of acidosis.

Recently it became apparent that excessive losses of NaCl and H_2O in the urine are important in the pathogenesis of renal insufficiency and lead finally to demineralization of the plasma and tissues. Thus renal tubular defects of opposite kind operate to disturb homeostasis of the electrolyte content of the blood.

The modern theory of dynamic exchange of metabolites with a body pool developed during studies of the protein metabolism; particularly those concerned with the fate of large protein molecules marked with deuterium and heavy nitrogen. The concept was summarized in this country for the most part by Whipple and Schoenheimer. Stability of body structures depends on a continual, fast-moving metabolic exchange, not only of simple metallic inorganic ions but also of complex organic molecules and chains of molecules. In the metabolism of proteins deamination, transamination and reamination occur with lightning-like speed. For instance, in cooperation with Dr.

From the Annual Meeting of the American Academy of Pediatrics, San Francisco, Calif., Nov. 15 and 16, 1949.

Schoenheimer's group, we were surprised to find that when glycine marked with heavy nitrogen was injected intravenously into hypoproteinemic dogs, a large fraction of the heavy nitrogen appeared in the ammonia excreted in the urine within 15 min.

The concept of dynamic exchange of electrolytes with body stores has also been in vogue for some years and recently has been fortified by studies with isotopic tracer elements. A continuous and active exchange takes place between the intracellular and extracellular fluids as well as with solid tissues such as bone.

The concept of a rapid dynamic exchange of metabolites with a body pool instead of slower equilibriums between plasma and fixed static reserve deposits such as fat stores, liver reserve deposits, the bones and others, forces us to re-evaluate the part played by the kidneys in the disturbances of biochemical homeostasis found in renal insufficiency.

The term "renal insufficiency" is loosely used to connote failure of the kidneys to maintain chemical homeostasis. Actually, the individual functions of the kidney may vary independently of each other; elevation of the NPN in the blood often occurs long before concomitant disturbances in the acid-base balance appears. The loss of ability to concentrate urine is lost long before nitrogenous products accumulate in the blood. For the most part, however, multiple dysfunctions are noted simultaneously with varied sequelae.

The kidney is the main organ responsible for homeostasis and its prime function is to maintain the composition of the plasma at an optimal level. Although the manner in which such complicated reactions are governed by the kidney is still obscure as far as details are concerned, in the main, certain patterns have become more clear as time goes on. In health, the kidney regulates the exchange of metabolites so perfectly that the pH of the blood is kept within exceedingly narrow bounds, just on the alkaline side of neutrality. The plasma amino acid level barely fluctuates, and deviations of the various electrolytes and organic substances are quickly brought back within normal limits.

Elaborate studies of renal function have clarified many obscure relationships but a long vista still lies ahead and the manifold capacities of the renal tubular apparatus will undoubtedly confound us for many years to come.

Renal Hyperparathyroidism

The Ca, inorganic HPO_4, and protein of the plasma bear an intimate relationship to each other. Calcium exists in the plasma in three forms: a small amount which is completely ionized and highly diffusible; a large amount apparently bound to protein and relatively fixed and indiffusible; and an insignificant diffusible but not ionized amount bound in colloidal aggregates with organic acids, such as citric acid. Plasma inorganic HPO_4 is not bound to protein and is freely diffusible; a much larger portion of organic plasma P is bound to lipids and fatty acids. These complex phospholipids probably participate in base binding.

The concentration of inorganic HPO_4 ions in the plasma bears an inverse relationship to the concentration of ionized Ca, and both ions are in equilibrium with the $CaPO_4$ of the blood, in accord with the mass law. Although the reciprocal relationship of plasma Ca and plasma inorganic P is well documented, the reason for the causal relationship remains obscure. Without question parathormone, the parathyroid secretion, is responsible; yet the manner of action of the hormone is still controversial. Adherents of one group believe that parathormone acts directly on bone to mobilize Ca; the opposing belief is that parathormone lowers plasma HPO_4 by decreasing the amount resorbed from the renal tubules, that the lowered plasma HPO_4 results in elevated blood Ca which permits fixation in Ca-organic aggregates. Others believe that both these reactions occur and that the electrolyte disturbance in the blood is created by the disturbed $Ca:HPO_4$ ratio.

Although the main reservoir of Ca and P is in bone, both ions are active participants in the dynamic equilibriums of cellular activity. Phosphorus is particularly important in cellular metabolism, since inorganic HPO_4 is the chief anion in intracellular fluid. The organic phosphates of the cell are essential for muscular contraction, for phosphorylation in the intermediary metabolism of carbohydrates and for the metabolism of fats.

Even though the content of Ca and P in extracellular fluid is not great in amount, it is essential for the maintenance of normal neuromuscular control and the preservation of bone structure.

Plasma concentrations of ionized Ca and inorganic HPO_4 are regulated by the kidney and are dependent on a multitude of factors. Some of these factors have been studied intensively; integrity of the plasma concentrations of protein, pH and $H.HCO_3$ ion are especially important. Normal C-P

metabolism requires an adequate balanced dietary intake and proper intestinal absorption, for which vitamin D is essential.

To maintain a Ca-level of 10 mg./100 cc. plasma in children, the daily dietary consumption of Ca recommended by the National Research Council is 1 gm. The threshold for urinary excretion of Ca is a plasma concentration of about 7 mg./100 cc.; yet even with a daily consumption of Ca as low as 50 mg., some is excreted in the urine and a negative balance results.

Although the absolute composition of bone is not known, it is generally agreed that the basic inorganic matter is dahlite, composed of crystals of $CaPO_4$ and $CaCO_3$. Presumably, precipitation of these crystals depends on supersaturation of Ca, HPO_4, and carbonate ions in the tissue matrix. The enzyme alkaline phosphatase is an important adjunct to the formation of bone; it splits inorganic HPO_4 from organic HPO_4-complexes, and is found in significant amounts in the teeth, skeletal system, intestinal tract and the kidneys. Alkaline phosphatase is found in the teeth and bones wherever Ca is being deposited and, hence, in the absence of liver dysfunction, an elevated plasma alkaline phosphatase is indicative of active bone formation. In children, the normal level of plasma alkaline phosphatase is about 10 Bodansky units.

Another enzyme, phosphorylase, which may be an important dephosphorylyzing catalyst, has also been demonstrated in the growing cartilage of children and in bone tissue. Pathologic calcification may be expected to occur wherever an excess of HPO_4-ions occurs locally, together with an increase in the enzymes necessary for disintegration of organic P-moities.

Although Ca in the bone is in equilibrium with the plasma, the Ca of the teeth is bound in some obscure way; once a tooth has been calcified, little or no exchange with the plasma is possible. Decalcification of fully formed teeth does not transpire even if severe Ca-deficiency exists. Under duress, the teeth maintain their integrity in spite of extreme loss from the skeletal system.

The ratio of Ca to P in bone is approximately 2:1, so that the skeletal system contains a large store of P. The plasma contains only a small amount of P as inorganic HPO_4, while a large amount is bound to organic complexes. However, it is only the inorganic HPO_4 which is depleted if P-deficiency develops. Since the enzyme alkaline phosphatase has the power to release inorganic HPO_4 from the organic complexes in the plasma, a negative P-balance does not always mean loss of P from the bones.

Removal of the parathyroid glands in man leads to a decrease in the urinary excretion of P, elevation of the blood P, a fall in blood Ca, and finally decreased Ca-excretion in the urine. Reversal of this pattern occurs if parathyroid extract is administered to a normal man; excessive excretion of P in the urine, lowered blood HPO_4, elevated blood Ca, and finally excessive Ca-excretion in the urine.

Parathormone affects the HPO_4 dissolved in body fluids so that it is more readily excreted, resulting in a decrease in the serum P. The Ca:P ratio is disturbed, with increased resorption from the bony surfaces; this causes elevation of the serum Ca. The elevated serum Ca-level leads to increased urinary excretion of Ca, with depletion of the body fluids; bone dissolution compensates for this depletion, unless adequate amounts of Ca can be absorbed from the intestinal tract. As a result, more osteoid will be laid down and a vicious cycle results.

Lower Nephron Nephrosis

Lower nephron nephrosis is characterized by severe oliguria or anuria, the deposit of heme pigments in the tubules of the kidney, hypertension and uremia. In children it is seen after intravenous hemolysis associated with transfusion reactions, extensive burns, sulfonamide reactions, poisons and crushing injuries. Common to the numerous conditions associated with lower nephron nephrosis is shock.

Oliguria or anuria is heralded clinically by nausea, vomiting, weakness, pain in the abdomen or back. The urine passed is often bloody, smoky, or may be port-wine in color. Proteinuria of a moderate degree is usually present and the sediment contains granular or pigmented casts. Edema is usually insignificant.

If lower nephron nephrosis is associated with destruction of tissue and accompanied by vomiting and dehydration profound alterations in biochemical homeostasis occur. Shortly after the onset of oliguria, the blood pressure rises, NPN accumulates in the blood and acidosis can be established by chemical means; at times there is an increase in plasma K.

The mortality is high; about half of the cases of lower nephron nephrosis succumb within the

first week of anuria. Pulmonary edema is frequently seen at post mortem, and potassium intoxication may at times be the cause of death. In patients who survive, eventual recovery of the kidney is complete.

The pathogenesis of the renal lesion is thought to be due to vasoconstrictive ischemia which occurs with the onset of shock. Renal vasoconstriction is a general reaction of the body to unusual demands which interfere with the integrity of the circulation, such as extensive hemorrhage, traumatic injuries, coma and dehydration. The kidney can tolerate complete interruption of its arterial blood supply for about 30 min. without discernible injury, but when marked renal ischemia persists for longer than a few hours the tubular epithelium is damaged. Under such conditions a variety of renal dysfunctions arise, at times without demonstrable morphologic disruption of the tubular cells; uremia does not appear until later after the original inciting shock or injury has subsided.

The renal tubular cells lose their highly selective ability to reabsorb certain elements. Since glomerular filtration is diminished, and since there is often mechanical blockage of the tubule by deposited debris, electrolytes, H_2O, glucose and NPN may diffuse back into the plasma through the disorganized tubules. An important contributing factor in the persistence of anuria may be the decrease in effective filtration pressure consequent to the increased intrarenal pressure, but decapsulation is not universally effective for relief. Controversial is the part played by mechanical blockage of heme pigments or detritus from the injured tubular cells. Leakage of tubular urine through the damaged tubular epithelium is blamed for the anuria.

On pathologic examination the kidneys are swollen and greatly increased in weight; the medulla is dark colored and the cortex is pale. Microscopically there is relatively little disturbance in the glomeruli and proximal tubules, but localized areas of degeneration and necrosis of the distal segments are seen.

Although most investigators agree that renal anoxia is responsible for the syndrome the exact mechanisms of its production are not known. In oliguria, the urine is acid, and in the distal tubules a low pH is favorable soil for the precipitation of heme compounds; undoubtedly previous tissue injury facilitates the precipitation. Experimental studies show that deposited pigment may increase the severity of the tubular lesions.

Usually in sulfonamide intoxication the renal lesions are localized in the distal part of the nephron, yet diffuse injury may occur in many tissues of the body other than the kidney so that vascular lesions are widespread. Lesions in the distal tubule regenerate in from 7 to 14 days.

Azotemia in lower nephron nephrosis is due to impaired glomerular filtration, increased tubular reabsorption of N-products, and increased catabolism of protein initiated by tissue destruction brought on by the injury.

The majority of fatalities in lower nephron nephrosis occur about 6 days after the onset of anuria, and there is no correlation between the degree of azotemia and death. These facts suggest that a fatal termination is not due to the accumulation of waste products in the blood, but rather to disruption of the electrolyte pattern of the internal fluids. Diuresis usually begins after about one week of anuria, and the mortality is not nearly so high in patients who survive the first week of reduced urinary output.

Since the disturbances in lower nephron nephrosis are self limited and since the recuperative powers of the kidney are exceptionally great in children, a conservative program of treatment should be instituted; it should be designed to compensate for the loss of insensible perspiration without excess fluid which might cause edema particularly of the lungs, to compensate for the electrolyte loss, to spare catabolism of protein, and to prevent the ingestion of protein. Death has been known to follow the use of excessive fluids in adults.

In children without previous renal disease, drastic measures, such as decapsulation, removal of waste products in the blood by means of peritoneal irrigations, intestinal lavage or the artificial kidney, should be avoided until after 10 to 14 days of anuria.

The treatment of lower nephron nephrosis should be adjusted to the different phases of the disturbance; after suitable treatment of the initial shock, the basic principle of management of the anuric phase should be to limit fluids to meet the maintenance requirement. Enough fluid should be given to compensate for the insensible loss and the losses due to vomiting, diarrhea, Wangensteen drainage and so forth. Glucose should be administered to spare the catabolism of body protein. With the onset of diuresis tubular failure to reabsorb electrolytes from the glomerular filtrate may follow

a sudden loss of salts, clinically appreciable by the appearance of severe hypochloremia. To guard against this complication the blood Cl can be determined frequently to serve as a guide for proper restoration. With careful management, recovery of the kidney is always complete in the reversible cases. Chronic sequelae, insofar as the kidney is concerned, are not observed.

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Sodium and Potassium Excretion in Renal Disease

Dr. Richard W. Lippman: More than 30 years have passed since the study of renal function was revolutionized by the introduction of quantitative methods, first the Addis urea ratio, then the idea of "clearance," popularized by Rehberg and later by Van Slyke and his co-workers. During this time, clearance methods have been developed and extended to the measurement of individual renal functions, principally under the guidance of Homer W. Smith. But it is only in the last few years that a beginning has been made in the understanding of electrolyte excretion.

Excretion by the kidney is the net result of at least three processes: filtration through the glomerular membrane, secretion into the tubular urine, and reabsorption from the tubular urine. The glomerular filtrate has a huge volume, roughly 180 l./day in a normal man of average (70 kg.) size, and, except for the low protein concentration, is identical to plasma in its composition. Since ultimate urine excretion in such a man is only about 1 l./day, it is clear that most of the H_2O is reabsorbed, as the urine passes down the nephron. Since the glomerular filtrate volume each day is about 60 times the total plasma volume, if it were not for the equally massive reabsorption of water, man would rapidly be reduced to a desiccated protoplasmic powder.

Since Na- and K-ions pass freely through the glomerular membrane, determination of the plasma concentration and filtration rate enables one to estimate the filtered amounts. By difference from the net excretion, we can roughly estimate the amount of Na and K that is reabsorbed (Table I). From

TABLE I

Estimated Amounts of Electrolyte Ions Filtered and Reabsorbed by the Kidney

	Plasma conc. mg./100 ml.	Amt. filter. gm./24 hrs.	Amt. excret. gm./24 hrs.	Amt. reabsorb. gm./24 hrs.
Sodium	330	595	5	590
Potassium	18	32	0.5	31.5

these general facts, it can be seen, *a priori,* that the balance in electrolyte excretion is a delicate one, and that a relatively small change in tubular function, or in the balance between tubular function and glomerular filtration, may produce a greater effect upon the excretion of Na and K than a change in filtration alone of equivalent magnitude. In fact, one is struck by the tenacity with which this delicate balance is maintained until relatively late in the course of renal insufficiency, unless the blow suffered by the kidney, as in a devastating acute nephritis, is overwhelming.

From Table I, one might expect that renal disease affecting tubular function primarily would produce the greatest effect upon electrolyte excretion. Clinically, it is true that Na-excretion is diminished in the presence of a degenerative tubular lesion, whether resulting from nephrosis, renal lues, or the degenerative stage of glomerular nephritis. Furthermore, preponderant importance of the tubular lesion is demonstrated by the clinical similarity between these conditions, even though the filtration rate in nephrosis may often be normal or elevated, while in the degenerative stage of glomerular nephritis there may be a considerable decrease in the filtration rate.

Sodium Retention:

In the normal individual, Na is ingested and absorbed from the gut. Sodium is excreted principally in the urine, but in smaller amounts by sweating and in the feces. Absorption and excretion are balanced, so that the Na-content of the body is maintained at a more or less constant level. When the capacity of the renal tubules to excrete Na is diminished, ingestion and absorption exceed excretion, and the difference is retained with H_2O, as edema fluid. From this simple *schema,* one can approach the various methods for reducing Na-retention with its concomitant edema.

The most obvious step is to reduce intestinal absorption of Na. This may be done in two ways. One is to reduce the Na-content of the diet. The difficulties of reducing Na-consumption are well known to every practicing physician. Sodium lurks in many recesses of the dietary imagination, and those physicians who actually measure Na-, or Cl-, excretion realize the lengthy endeavor that may be necessary to obtain a satisfactory result.

A new method for reducing intestinal Na-absorption has been introduced with the use of ion-exchange resins. These complex resins, produced from a variety of precursors, have the property of exchanging one ion for another with readiness and specificity. Those in current investigational use exchange H or HH_3-ion for Na and K. While Ca is also removed from salt solutions *in vitro*, the resins have not been found to increase Ca-excretion, making it seem probable that Ca in the intestinal tract is not free to combine with the resin.

The effectiveness of ion-exchange resins is almost miraculous in many instances. As an example, one adult patient had been virtually bed-ridden with massive anasarca, due to the nephrotic syndrome of glomercular nephritis, for nearly 3 years. All the usual diuretic measures had been exhausted without benefit. He was given increasing doses of ion-exchange resin* until diuresis occurred, when he was receiving 48 gm., divided in 4 doses through the day. He lost approximately 18.1 kg. in 3 weeks and was able to resume normal limited activity.

Since the resin may remove not only ingested Na and K, but also that secreted by the gastrointestinal glands, care must be exercised to prevent the occurrence of Na- and K-deficiency. It is advisable to question the adult patient for symptoms of such deficiency and to determine the serum Na- and K-concentrations at frequent intervals until regulation is achieved.

The alternative way of reducing Na-retention is to increase excretion. This may be done by way of the sweat. A Turkish bath has been known to reduce edema since ancient times; a patient in the nephrotic syndrome occasionally rediscovers this fact and uses it for his benefit.

Sodium excretion may be increased through the feces, as in diarrhea. Sodium loss in this manner may approach considerable magnitude, as in the nephrotic syndrome. However, Na-loss, with its associated loss of K, is a real danger in the infantile diarrheas.

Finally, Na-excretion may be increased through the urine, in several ways. One way is to diminish tubular capacity for reabsorbing Na and H_2O by means of tubular poisons. Such substances include the xanthine and mercurial diuretics. It seems illogical to use tubular depressants in the presence of tubular disease. Recent work has shown that, in rats, the toxic action of mercurial diuretics, observable even when the dose approaches equivalence to that used therapeutically in man, can be prevented by the induction of proteinuria. Such a finding suggests an explanation for the apparent innocuousness of mercurial diuretics in the presence of renal disease, and for the frequent ineffectiveness of mercurial diuretics in the presence of proteinuria.

Urinary Na-excretion may be increased through the use of osmotically active agents. Concentrated, salt-poor, human albumin has been used commonly since its development as a plasma substitute during the war. Most clinicians have been disappointed with the results. Albumin administration causes a transient increase in plasma volume and glomerular filtration rate. The results are irregular, evanescent and expensive. Albumin administration in the nephrotic syndrome is associated with an almost quantitative excretion of administered protein in the urine. Notwithstanding the work of Baxter and Cotzias in rats, there remains the possibility of danger from the high urinary protein concentration. After albumin administration, increased numbers of tubule cells die and can be seen as desquamated cells in the urinary sediment. There is increased cast formation, and it is possible that this circumstance may lead to the blocking of additional nephrons.

Mannitol has been used to increase the osmotic activity of the tubular urine, since it is filtered by the glomerulus, and, if any, a very small fraction is reabsorbed. Urea as a diuretic is mentioned only to be condemned. The excretion of urea, although it may produce diuresis, places a great additional load of osmotic work upon the kidney, and there is no place for the use of urea in the presence of renal disease.

The regulation of electrolyte excretion is not clearly understood. Sodium, after filtration by the glomerulus, is reabsorbed by the proximal tubule in a relatively fixed proportion of the filtered quantity, regardless of the absolute amount filtered, within physiologic limits. In contrast, reabsorption by the distal tubule, although accounting for only about ⅛ of the total reabsorption, is variable and

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* Supplied through the courtesy of Winthrop-Stearns, Inc., as Win 3000.

subject to influence by such agents as the pituitary antidiuretic hormone and the adrenal cortical steroids. The latter circumstances offer the opportunity for a different approach to the induction of diuresis. Diuresis might be obtained through the inactivation of antidiuretic principles, through the production of antibodies to the antidiuretic hormone, to the adrenocorticotropic hormone, or to the adrenal cortical steroids themselves. Inhibition of adrenal salt-retaining steroids might be secured by the administration of non-salt-retaining steroids, such as Compound A. Experiments to determine the feasibility of such measures are at present being performed.

Fox and McCune have advocated the administration of Na- and K-salts in large doses to children with nephrosis in the belief that an elevated plasma Na-concentration would move H_2O out of the cells, increasing plasma volume and consequently glomerular filtration. Potassium was given in order to permit replacement in cells as the total osmotic pressure of extracellular fluid was raised by Na-administration. In their figures, no convincing change in plasma Na-concentration is observed, and the diuresis is not associated with a rise in plasma volume, as indicated by the hematocrit value. The administration of large doses of Na and K to such patients is certainly associated with risk and does not seem justifiable for general practice without further investigation.

Sodium Loss:

Excessive dietary Na-restriction may lead to disaster in the presence of renal insufficiency. It is not clear why the kidney, which at one stage cannot excrete Na, occasionally cannot retain Na after the onset of gross renal decompensation. The term coined by Thorn, "salt-losing nephritis," seems inadequate, as it diverts attention from the fact that inability to retain Na is not characteristic of some peculiar and specific renal inflammatory disease, but may be associated with renal insufficiency, regardless of the etiologic agent.

Sodium depletion, resulting from prolonged dietary restriction, especially when combined with the use of diuretics, may actually initiate clinical renal failure. It seems likely that renal failure in such instances accompanies shock, with reduction in plasma volume and renal ischemia. Since the reported cases have occurred in the course of treating cardiac failure, often the result of hypertensive cardiovascular disease, it is reasonable to suppose that nephrosclerosis and chronic passive congestion had previously lowered the renal functional reserve. Conn has suggested that, under these circumstances, the adrenal glands may be laboring to produce an additional supply of the cortical steroids that aid in conserving Na. This functional over-activity might be nonspecific, with overproduction of steroids responsible for increasing protein catabolism, consequently increasing the functional load on the kidney.

Potassium Retention and Loss:

Many recent papers have emphasized the clinical importance of K-balance in chronic diseases with electrolyte loss, and in glomerular nephritis. Reduced serum K-concentration may also occur during the renal ischemia syndrome ("lower nephron nephrosis") if treatment by artificial dialysis is used, unless the effect upon electrolyte balance is carefully followed and corrected.

While the loss of K is frequently a serious problem in the infantile diarrheas, as emphasized by Darrow and co-workers, and in some surgical conditions associated with loss of intestinal secretions, it is an infrequent finding in chronic renal disease with renal failure. Occasionally, however, uncontrollable cardiac failure and muscular weakness in adult patients with uremia may result from K-deficiency, and response to K-administration may be dramatic.

Accumulation of K in patients with renal failure is a much commoner clinical finding, and evidence of K-intoxication is often observed. Unfortunately, this situation is not easily corrected.

Conclusions

By considering the mechanisms of Na-balance systematically, it is possible to derive a rational approach to the restoration of balance, with relief of edema, in the presence of renal disease. The most promising approach, at the present time, utilizes Na-adsorbent ion-exchange resin. The possibility of immunologic neutralization of the biologic antidiuretic substances offers further hope, after further investigation.

Recent work has emphasized the importance of K-balance in the presence of impaired renal function. It is especially important to remember this when instituting measures, such as those mentioned, which substantially alter the rate at which electrolytes are absorbed and excreted.

* * *

Dr. John A. Luetscher, Jr.: Dr. Goettsch has pointed out the importance of limitation of H_2O and of Na-intake during the anuric stage of lower nephron nephrosis. However, during the stage of diuresis after the acute renal tubular injury, one sees all varieties of dissociation of salt and water excretion. Ordinarily, one sees a loss of Na and H_2O in the urine during this stage, with some dehydration and sometimes with a fall in the serum Na- and Cl-concentrations. Less commonly, we have seen patients, following sulfonamide poisoning with anuria, develop a syndrome of loss of water without Na, with dehydration and a high serum Na-concentration. We were baffled by the first patient of this type whom we observed. After 10 days of anuria, he began to have a diuresis. As the urine volume increased, the Cl-concentration of his serum, which had been subnormal, was noted to rise to a little bit above normal levels. The patient seemed to be getting better, but he gradually became dehydrated. We gave him some isotonic NaCl without any improvement in the dehydration. On the 5th day after diuresis began, we were astonished to find the serum Cl-concentration above 130 mEq./l. Without any further intake of NaCl, his Cl-concentration continued to rise to nearly 150 mEq./l. It was only then that we realized that instead of losing NaCl in the urine, this patient was putting out almost no Na in the urine. At the same time, he was pouring out H_2O, so that he was becoming dehydrated while retaining NaCl.

Such patients demonstrate that when renal function is seriously impaired, it is not practical to depend on the kidney to maintain a normal Na-concentration in the extracellular fluid. In the case just described, the kidney retained Na without H_2O. More commonly, the damaged kidney will retain H_2O without Na, so that the Na-concentration of the serum falls. In this situation, a salt-free diet may fail to help the edematous patient, and will lead to hypochloremia, hyponatremia, and further impairment of renal function. It is therefore important to follow the serum Na- or Cl-concentration whenever we try to remove H_2O by eliminating salt.

With these precautions, the use of an Na-free diet or of an ion-exchange resin is probably the simplest and least harmful measure for the relief of edema. Most patients with the nephrotic syndrome have good enough renal function to maintain an only slightly subnormal serum Na-concentration. There are patients who are resistant to these measures, however, and then we must turn to some method of increasing Na-excretion. This is not always easy. Dr. Lippman's orderly analysis of the possible routes of elimination of Na including sweating and purgation. Although these possibilities exist, they are unpleasant, fatiguing, and rarely effectual enough to warrant consideration. Southey's tubes are probably the most harmless and effective method of removal of edema in adults, though they are confining and more difficult to keep in order in children.

In addition to these possibilities of extra-renal Na-elimination, the idea of increasing renal Na-excretion toward normal remains most attractive. Some agents for this purpose are available, but each of the effective agents is under suspicion as a possible cause of renal fatigue or damage. Dr. Goettsch has emphasized the most important concept, that we must not treat the symptom, edema, with methods which may lose the whole campaign because of renal failure. Nevertheless, we should examine the rationale, the effectiveness and the toxic effects of possible treatments with an open mind, and judge them according to clinical results, not on the basis of any particular theory or of some inconsequential side-action.

A few years ago, most descriptions of the nephrotic syndrome emphasized the sequence of proteinuria, hypoproteinemia, reduced colloid osmotic activity of the plasma, and escape of fluid from the capillaries. Although the textbooks were quite clear, many students of the disease did not accept this explanation as adequate. The inability of the severe nephrotic to excrete Na in normal amounts had been observed, but the relationship of Na-retention with the protein deficiency remained unclear. A few observations may help to clarify some aspects of this question.

The first patient whom we studied had a cyclic form of nephrosis with repeated exacerbations of edema and proteinuria, alternating with periods of profuse diuresis and diminution of proteinuria. We were surprised to find that his lowest plasma protein concentration occurred quite regularly on the first day of diuresis, and that his highest plasma protein concentration was regularly noted on the first day of beginning relapse. This made nonsense when one tried to explain the edema on the basis of the changes in the plasma osmotic pressure. The only rational explanation was that the plasma was diluted by the edema. This dilution was confirmed by the trend in plasma volume, which was largest when the protein concentration was lowest, just at the onset of diuresis. Variations in proteinuria had less effect on plasma protein concentration than the dilution.

We then measured the effects of infusions of concentrated human serum albumin on the hypoproteinemia and edema of the nephrotic syndrome. Injections of albumin were followed by a temporary, often total replacement of the deficit in circulating albumin. In 40% of our cases, the result was a complete relief of edema and an increase in the concentration of serum albumin. These patients were then maintained edema-free for weeks to months on a low-Na diet. Half of our patients failed to obtain any real relief of their edema. These patients showed a remarkable dilution of injected albumin by "mobilized" edema fluid, but since the kidneys failed to excrete the fluid, the concentration of the plasma proteins could not be increased significantly. Just as in the observations of spontaneous changes in nephrotics, we observe here the vicious circle of edema and hypoproteinemia, each aggravating the other when fluid is retained by the kidneys, and both being improved when the kidneys excrete the excess of fluid. Because of its striking effect on blood volume, we hesitate to use albumin when there is appreciable hypertension or cardiac enlargement.

I would take issue with Dr. Lippman on 3 of his statements about albumin, but I am glad that he has brought these points up for consideration. It was stated that albumin is quantitatively lost in the urine. Such an event occurs uncommonly, and then only after several days of treatment of the most severe types of nephrosis. In the meantime, even these difficult cases have retained a considerable amount of albumin, and there is frequently an almost complete replacement of circulating albumin, even though masked by dilution. The milder cases retain albumin fairly efficiently, losing as little as 20% of the injected albumin in the urine. Dr. Lippman classified albumin as an osmotic diuretic: we can state categorically that this is not the case, since the osmolarity of the urine falls when albumin is given, and since the diuresis bears no consistent relationship to the amount of proteinuria. The diuretic effect of albumin is apparently exerted by an increased blood volume and by an improvement in renal function. Dr. Lippman's description of droplets in the epithelial cells of the urinary sediment can hardly be interpreted in patients with the nephrotic syndrome, who commonly show such changes spontaneously. I share Dr. Lippman's reservations about prolonged, heavy proteinuria, however, and I do not like to give albumin for more than 4 to 6 days at a time. With this regime, all evidence points to an improvement in renal function. The blood NPN falls, and various indices of renal function can be shown to increase. No satisfactory evidence has yet been presented that even prolonged treatment with albumin has had any effect on the ultimate outlook of the patient. Albumin is not a panacea, but it is a rational and often a helpful form of treatment of the nephrotic stage.

If we replace the albumin deficit in a nephrotic patient and fail to get a diuresis, we wonder about the reason for the tenacious renal retention of Na and H_2O. In some cases, Na and H_2O are retained because of renal injury or reduced glomerular filtration rate. In other cases, renal function and filtration rate are well maintained or even supranormal, and we must assume that renal tubular reabsorption of Na is increased. A possible stimulus for Na-reabsorption might come from the reduced serum Na-concentration which is present in certain cases, particularly after prolonged salt deprivation. Dr. Charles Fox has suggested that the administration of Na- and K-lactates may be helpful. We have had little experience with his method, which deserves further study. Alkalosis and aggravation of edema are possible complications. Another possible stimulus to Na-reabsorption may be the reduced blood volume. The patient with nephrosis must maintain his circulation with a severely reduced amount of circulating protein, and this can only be done by establishing a relative hydremia. A possible mediator in this compensation is the adrenal cortex, which can be activated by a fall in blood volume. Dr. Quentin Deming has developed a bioassay method for the measurement of desoxycorticosterone-like steroids in the urine. In some preliminary studies, we have found a rough parallelism between the severity of the edema and the level of Na-retaining factors present in nephrotics' urine. Possible modification of such excessive adrenal activity deserves investigation.

The conventional diuretics have a very limited application in the treatment of the nephrotic syndrome. They are often ineffectual and sometimes dangerous. I have a strong prejudice against the use of the mercurial diuretics in patients with renal disease. When more is understood about the pathologic physiology of nephrosis, there is hope that an effective method of treatment may be found.

* * *

DISCUSSION

Dr. Luetscher (answering Dr. Randolph G. Flood, San Francisco, on sodium and potassium

salts): Nephrotics fall generally into 2 classes. The first type is the milder case, in whom it is possible to induce a good urine flow by administration of H_2O. This patient's problem is apparently in the excretion of Na. He has good enough renal function to maintain his serum Na-concentration normal even under the stress of a high H_2O-intake and very little Na-intake. Under these circumstances, restriction of Na in the diet will result in more or less reduction in edema, without risk of complications.

The second type is a more severe form of the disease, with massive edema and heavy proteinuria. Unfortunately, many children show this form of the nephrotic syndrome. In these cases, administration of large quantities of H_2O, much out of proportion to the Na intake, results in the accumulation of fluid in the body and in the development of a hypotonicity of the body fluids. Here we have a problem which is somewhat like that of a patient with severe oliguria due to acute renal damage. Moreover, when the serum Na-concentration falls to a low level, even though there is an excess of H_2O in the body, the kidney becomes refractory to its excretion, and renal function is impaired in other ways. The specific remedy is the administration of NaCl but, in the nephrotic patient, this may lead only to further fluid retention. Dr. Charles Fox has suggested that the use of Na-lactate, together with a restriction of Cl-intake, may solve this dilemma. If renal function is good enough, and if the patient can tolerate some alkalosis, the Na-concentration might be brought up to normal without undue increase in the edema. It is a good idea, but I have had very little opportunity to try it, and so would not presume to comment on the results.

Dr. Flood: In our studies of the transmethylation defect in the nephrotic syndrome we have been interested in the electrolyte pattern in these cases. The children are usually seen by us after the edema has persisted for a variable period of time. Their presenting electrolyte picture is one in which the plasma Na is reduced below normal, usually below 125 mEq., the plasma HCO_3 is markedly reduced and there is a retention of Q. The urine is reduced in amounts, there is practically no Na but the urinary K is increased often to 90-100 Eq.

Following Fox's suggestion, we tried to correct this imbalance of electrolytes by giving Na-K acetate to raise the plasma Na to above 140 mEq. This was associated with an initial increase in body weight followed by a marked increase of urinary Na often followed by a massive diuresis.

The edema in the nephrotics must be considered as only a symptom. The true etiology is still unknown. We have demonstrated in our two previous papers that there is a defect in the creatine metabolism, in that glycocyamine which is formed in the renal tissue is not properly methylated in the liver to form methyl glycocyamine or creatine.

We are now substantiating this claim of defective methylation in the study of the metabolism of nicotinamide. This is methylated in the liver to form N-methylnicotinamide and 6-pyridone N-methylnicotinamide in about equal amounts in the liver. Quantitative measurements of these two substances show that the nephrotic does not methylate nicotinamide any better than glycocyamine.

Dr. Luetscher: In the most severe cases what happens is that in the first 2 or 3 days, and as long as you care to give albumin to patients in the very mild cases, there is retention of protein as such. One sees less in the urine than one is giving. Then, in the most severe cases after the first few days one sees almost quantitative excretion of the albumin which was injected into the urine. The globulin excretion is hardly affected at all. Then what happens to that albumin which is retained? The same thing happens to it as with any protein plasma which is injected into the body whether with a normal or a nephrotic. A certain amount is stored, a certain amount is retained in the plasma. That which goes into the cells will then, over the course of the next 2 weeks, appear as excess, if the patient is on a balanced regime as excess NPN. In other words, it is metabolized very slowly. This also has an important side issue and that is if one has a patient who has a temporary renal insufficiency, in whom it is desired to raise the serum protein concentration without putting an added load on the kidney. With the injection of albumin one sees a delayed metabolism for about 2 weeks so that you can get the protein into the patient that way without having to pay for it in terms of increased nitrogenous waste.

Dr. Henry L. Barnett, New York City: I would emphasize the dangers which Dr. Luetscher has pointed out in the use of this rather drastic treatment. They are such that it should not be employed in circumstances other than those in which very careful following of the whole picture is possible because in the experience of some other people disastrous results have occurred. On the other hand, the treatment is well worth considering.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy

INTRODUCTION

DR. ERNEST L. STEBBINS, whose communication appears below, is Professor of Public Health Administration and Director of the Johns Hopkins University School of Hygiene and Public Health. He has previously worked as epidemiologist and District Health Officer in State Health Departments and has held the position of Assistant Commissioner of Health in New York State and Commissioner of Health in New York City. He was at one time professor of epidemiology at Columbia University. He is secretary of the American Board of Preventive Medicine and Public Health and holds numerous other committee and board memberships.

COMMUNICATION FROM DR. ERNEST L. STEBBINS

DEAR DR. HARPER:

Some time ago you suggested that I formulate some of the ideas which we discussed concerning the provision of adequate medical care for the so-called medically indigent. I am of the firm belief that in the greater part of the United States the provision of adequate medical care for this group is one of our most serious problems. Unfortunately, in spite of what appears to be quite general recognition of the urgency of this problem, I know of no place that has developed a satisfactory solution to this problem.

One of the most difficult problems is the definition of the medically indigent and the determination of the magnitude of the group. Medical indigency is usually described in terms of an economic level permitting the provision of the necessities of life under normal conditions and the reasonable provision of medical services independently, except in the case of severe or prolonged illness requiring costly medical services or hospitalization.

The actual income level per family and the range of such income which will provide for these ordinary necessities of life is a much disputed point and unquestionably varies somewhat in different parts of the country. The annual income which provides these minimal essentials ranges from a low of approximately $1800 to a high of $3500 or even higher for the average family. The proportion of the population falling within the level agreed to be medically indigent is variously estimated at from 20 to 50% or higher. Whatever figure is accepted, it is a very significant proportion of the population.

The frequency of severe or prolonged illness in this group has not been accurately determined to my knowledge. It is known with certainty however that the frequency of illness and disabling conditions is higher in this income level than in groups of higher income. Even a casual review of hospital and social service records impresses one with the frequency of illness as a major factor in producing true indigency in families formerly able to maintain the necessities of life by independent effort.

It is frequently suggested that voluntary medical care insurance is a solution to the problem of this large group. Unfortunately, there is no evidence that voluntary medical insurance has received wide acceptance among those in the income level most in need of some means of protection against the financial burden of catastrophic illness. Various reasons have been given for this lack of acceptance of voluntary prepayment medical care insurance. Uncertainty of employment at these income levels is not infrequent, and improvidence and lack of a sense of responsibility is a frequent charge. Expenditures for luxuries such as cigarettes, alcoholic beverages, automobiles and radios would seem to be an indication of this lack of a sense of responsibility to provide for necessary medical services, particularly in time of severe and prolonged illness.

Whatever the cause and wherever lies the responsibility for this situation, what is the result of the failure on the part of the individual to provide through savings or through insurance to meet the cost of serious and prolonged illness?

First, necessary medical care is not infrequently delayed to the point of increasing the severity of the illness, and eventually increasing the cost of medical care, however provided. Second, in most communities governmental assistance in the provision of medical care is withheld until all of the individual's resources have been exhausted, reducing the family to complete indigency. At this point governmental assistance is given, all too frequently delayed until the necessary treatment is prolonged, and the likelihood of complete recovery reduced, all of which increases the public burden. This series of events is certainly not to the advantage of the individual, nor to the taxpayer.

One might well ask at this point what then is the solution to the problem of the medically indigent? There seems to be general agreement that at least a significant proportion of those who would be classed as medically indigent could provide at least a major proportion of the cost of medical care if these costs were distributed in time through some method of insurance.

Experience would seem to indicate that voluntary insurance does not appeal to the majority of those in the lower income levels. Perhaps in the millennium there will be a general feeling of personal responsibility that would lead to general acceptance of voluntary medical care insurance. In the meantime what inducement can there be to prevail upon this group to make provision for the illnesses to which they are especially prone? Compulsion is an unpleasant word, and apparently particularly as it relates to medical care insurance.

The payment of taxes has not always been considered an unmitigated blessing, and it was considered necessary by the government, in order to assure payment of taxes in the low income group, to provide for payroll deductions. More and more the improvidence of the human race has been recognized and even the philanthropic organizations are tending more and more to rely upon payroll deductions to assure contributions to worthy causes. One cannot but wonder why it is so different or why one should lose so much more in liberty and independence if assurance of adequate medical care for the low income group were to be provided through the same means.

Under a system of compulsory medical care insurance for low income groups, providing for payroll deductions and administered by state and local governments, more adequate medical service should be possible, and quite possibly at less total cost than the service now rendered after the individual has been forced into indigency by illness, the serious nature of which might well have been prevented by early care. One might well ask, how much are we willing to pay, not only in dollars, but in human suffering, to avoid that evil word "compulsory"?

(signed) ERNEST L. STEBBINS, M.D.
Baltimore

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

AT THE Annual Meeting of the Academy in San Francisco, the status and functions of the ICH Committee were presented in a panel discussion by members of the Committee and its executive staff. Dr. James L. Wilson, who for three years has served as Committee Chairman, called attention in the following cogent statement to some of the problems of immediate importance:

"The background of the ICH Committee is so recent and its function and actions have been so much discussed that it should be familiar to all of you. It was formed, as I am sure you realize, not by any of its original members but by the President and the Executive Board, acting in a state of healthy experimental confusion which was natural, but with an ideal and praiseworthy purpose. That purpose was to act as a fact-finding and analyzing agency with special regard to the data derived from the Study of Child Health Services and thus to assist the Board and the Academy as a whole in taking effective steps to improve child health in this country. The need for such a committee was based wholly on the concept that the Academy should function as an aggressive and independent body to express authoritative opinion and exert influence about public affairs that bear on child health. If the conception is held that the Academy should be only a scientific body, to hold meetings for self education with no intent to influence public opinion or the action of other bodies, then there was no need for the survey nor for such a committee. I hope that the attitude which really underlay the foundation of the Academy itself continues and that the Academy keeps itself in such a position that it can criticize activities bearing on child health but at the same time be able to offer positive ideas as substitutes for those that it criticizes.

"The immediate problem that the ICH Committee faces is to aid the Academy in developing and publishing an interpretive analysis of the defects in child health care revealed by the survey, and to offer broad recommendations for treatments of these defects at the national level, while state and local action is left up to individual states and communities. Our state chairmen and other members of the Academy have already received copies of a preliminary and tentative attempt at such an analysis. This first effort does not represent any finished product nor even the unanimous opinion of all members of the Committee on all points. This is as it should be since it is offered to the Academy through the state chairmen only as a basis for your study and as an attempt to entice eventually from you all both positive and negative criticisms. Only by this means can it possibly be completed and published as representing an Academy stand backed by the great majority of the members.

"It has been stated that the Academy of Pediatrics is too large an organization to be able to follow democratic procedures and yet preserve effective action. We face this challenge now in regard to the interpretive report and recommendations. Since the

influence which we have gained from the survey will soon be lost unless effective and positive action is taken, some urgency exists for the completion of this task and a definition of a public stand by the Academy on many controversial matters. The ICH Committee itself could quickly complete an interpretive analysis of the survey with recommendations, but I am certain that you agree that it should not and obviously could not assume the whole responsibility for composing this important report, and can only aid the Academy as a whole in doing it.

"The Academy will find itself in an awkward position if it cannot express concerted opinion that will be much more than a series of platitudes. And, above all, we must avoid finding ourselves in the position of having carried out this great survey to be used by governmental agencies and other organizations while we ourselves are unable to produce anything effective or convincing to those who want to change the American way of life, except perhaps to state that we want no change. I hope we can succeed through democratic action in doing more than that.

"The ICH Committee, particularly, needs guidance concerning the scope of the general recommendations which should follow the interpretation of the survey in our Academy report. Should other crucially important matters related to child health be considered in addition to those covered in the survey? Great as it was, the survey was necessarily limited in extent and we are all familiar with many acute and serious problems which were hardly mentioned and were not studied. With no attempt here at completeness, I can mention as illustrations two or three controversial questions not directly dealt with in the survey but of importance to pediatrics and regarding which the Academy might exert a beneficial influence.

The shortage of specially trained pediatric nurses, as well as all nursing personnel, makes the hospitalization of sick infants in many places even dangerous and almost cancels out its value.

The question whether medical charity should be distributed to people on the basis of their financial means and with or without partial payment by the recipients underlies many of the problems which are being brought up in Congress or at state levels, and which affect the medical profession and so, the pediatricians. Can the Academy take a stand on this?

Should the Academy take any steps to encourage organization of more efficient cooperative practices in the care of children? Should the Academy encourage the development of Health Clinics where the members themselves may carry on their practice associated with hospitals, where complete infant and child health care for the community can be offered? Should it instead encourage the further development of complete health services to children in the schools or in well baby clinics?

"Matters related to pediatric education have already been considered by the Academy and action taken, since the part of the survey dealing with education was completed first and first offered us the opportunity for specific positive recommendations. Recommendations for support of educational institutions by the federal government have been made but action regarding them has been held in abeyance until efforts of the AMA to raise private funds could be determined as successful or not. Eventually, and I think soon, the Academy must again take its stand on this matter or be found in the unflattering position of complete indecision.

"At this moment particularly, the ICH Committee is in an awkward situation since it has made commitments and plans for the future at a time when plans for reorganization of the administration of the whole Academy are being seriously considered. The raising of money to support the work of the Committee and, therefore, the Academy for such charitable purposes as aid to pediatric education through the development of meetings of

pediatric educators for study of teaching technics, has been seriously handicapped by general knowledge that reorganization of the Academy is imminent and the present function of the ICH Committee and its staff is on a temporary basis. Already some highly profitable meetings on pediatric education have been held. It must be remembered that there is no organization in this country on the national level that has expressed a primary interest in technics and resources of pediatric education and the Academy can do an enormous amount of good if it assumes direction and gives aid in this matter. However, as I have said, further action will be handicapped until a plan for reorganization, if it is to take place, is agreed upon and the basis of our activities clarified.

"Our Committee agrees that its composition, organization and even its function should be subject to radical revision. We feel that the present status of the Committee is illogical and has been confusing, although I think it has served a very useful purpose in enabling us to get acquainted with ourselves and our problems during the last few years. The various controversial points that have arisen have been extremely valuable in our own self education. The Committee looks ahead to its own demise with definite approval which it has expressed to the Board, but strongly feels that the basic purposes for which it was originally formed should be considered in the reorganization and that its basic duties should be carried on within the Academy and not be dropped at the termination of the duties of the Committee and its executive personnel."

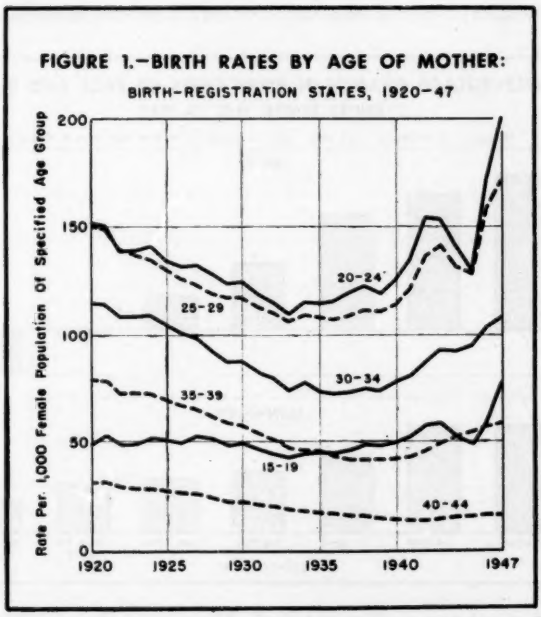
PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

RECENT TRENDS IN BIRTH RATES IN RELATION TO AGE AND BIRTH ORDER

PEDIATRICIANS early felt the effect of the tremendous increase in births in recent years. It comes as no surprise to them to see that a great portion of this increase was associated with young mothers and primiparae who presented a more difficult and time-consuming task in relation to health supervision.

Figure 1* demonstrates that the increased total birth rate has by no means been due to young mothers alone although the major rise has been in mothers under 35 years of age. The rates for all age groups over 20 showed steady declines from the beginning of this chart, 1920, probably as part of a long time trend, and all under 30 reached their



lowest point toward the end of the great depression in 1933. The older age groups showed an upturn in successively later years although none over 30 reached the 1920 level.

Between 1940 and 1947 the rates for women 15 to 29 years of age fluctuated more extremely than did those for the older women. As might be expected, economic and

* National Office of Vital Statistics, Public Health Service, Federal Security Agency. Vital Statistics—Special Reports, vol. 31, no. 15, Nov. 2, 1949.

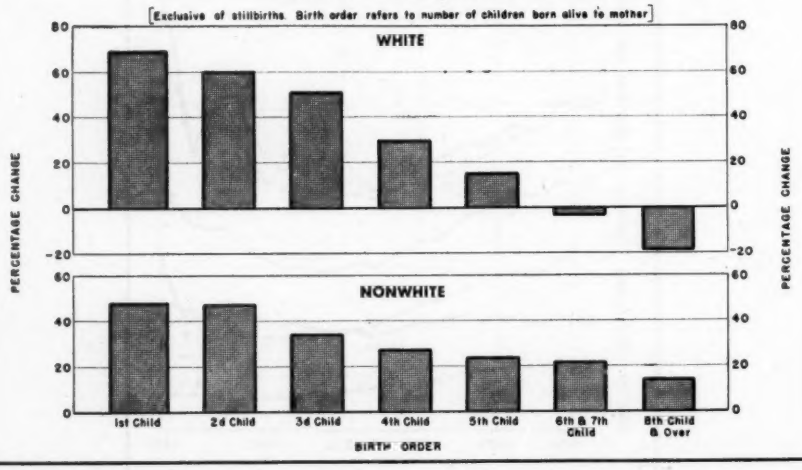
psychologic factors related to the war had a more immediate effect on fertility among women under 30 years of age, and the birth rates in these age groups show a sudden upswing from 1940 to 1943. The declines in the rates for young women in 1944 and 1945 reflect the prolonged absence of millions of men on overseas duty, while the sharp increases which occurred in 1946 and 1947 followed the rapid demobilization of the armed forces at the end of 1945 and early 1946. The spectacular rise in the birth rates for women under 30 years of age during this postwar period brought these rates considerably above the corresponding rates in 1933 and well above the rates following World War I.

Despite the increases that occurred during the war and postwar years in the rates for women aged 30 to 44 years, in 1947 the rates for these groups remained substantially below the comparable 1920 rates. For 30 to 34 year old women the 1947 rate was 7% below that for 1920, for the 35 to 39 year group there was a drop of about 27%, while the 1947 rate for the age group 40 to 44 was only slightly more than half of the corresponding 1920 rate.

While age of mother has clearly been an important influence, birth order needs to be considered in relation to age. In general, of course, the younger mothers will be the primiparae but a study of the trend of birth rates in relation to birth order is necessary if one wishes to draw any conclusions concerning family size and the general reproduction rate of the population. Figure 2 illustrates, for both white and nonwhite population, the

FIGURE 2.–PERCENTAGE CHANGE IN BIRTH RATES BY RACE AND BIRTH ORDER: UNITED STATES, 1940 TO 1947

[Exclusive of stillbirths. Birth order refers to number of children born alive to mother]



extent of the change between 1940 and 1947. The general characteristics of the changes are similar for both white and nonwhite population, although the latter shows a less striking increase in the rates for the lower birth orders, and, conversely, fails to show the decline present in the higher birth orders among the white population.

Numerically, the 1947 rates for the low birth orders represent the starting of almost 1.5 million white and nonwhite families, the addition of a second child in close to a million families, and of a third in about half a million families. Of the total number of

children born to white women in 1947, two thirds were first or second births as compared with about half among nonwhite.

During World War II, the rate for first order births among white women reached a peak in 1942 and then declined through 1945. The rise in the rate during the postwar period brought the 1947 rate for first order births to a point almost 70% above the 1940 rate. The rates for second through fourth order births also did not increase continuously throughout the war years, but they were at a higher level in 1945 than in 1940. Further increases occurred in the postwar period, and by 1947 the second and third birth order rates for white women were more than 50%, and the rate for fourth order births was almost 30% above the corresponding 1940 figures.

Another point of interest is that the 1947 rates for each of the first two birth orders among white women were higher than the corresponding figures in the years immediately following World War I. On the other hand, the 1947 rate for fourth order births was still about a third below the comparable rates of 25 or 26 years ago; rates in higher birth orders were one half to one third of those in the earlier period.

It is possible that continuation of the changes shown will result in reversal of the long time trend toward small families. To a considerable extent socio-economic factors will determine whether such a reversal is possible although it is doubtful that such reversal is to be expected under the present day mores of our country.

NEWS AND ANNOUNCEMENTS

The International Society of Hematology will hold its Biennial Congress at the University of Cambridge, Cambridge, England, from Aug. 21 through 26, 1950.

The Program Committee is in the process of receiving titles for papers and scientific exhibits to be presented at the Congress. Material to be submitted for consideration for the program may be sent to Dr. I. Davidsohn, Mt. Sinai Hospital, Chicago, Ill., or Dr. S. Mettier, University of California, San Francisco, Calif. Those desiring to present scientific exhibits should make application as soon as possible.

* * *

A continuation course in pediatrics for general physicians will be presented at the Center for Continuation Study of the University of Minnesota from Jan. 26 to 28, 1950. The course will be divided into three major divisions. A short period will be devoted to the importance of hereditary and genetic factors in understanding pediatric problems. A second portion of the course will emphasize common dermatologic problems seen in infants and children. Common infectious diseases will be considered in the third portion of the course. Dr. Franklin H. Top of the Herman Kiefer Hospital, Detroit, Mich., will be the visiting faculty member for the course.

* * *

The American Academy for Cerebral Palsy announces that its annual meeting will be held in New York City at the Waldorf-Astoria Hotel on Friday and Saturday, Feb. 17 and 18, 1950, immediately following the meeting of the American Academy of Orthopaedics.

Scientific sessions will be open to visiting orthopaedic men and any other physicians interested in the problem of cerebral palsy. All phases of cerebral palsy will be discussed.

* * *

The American Board of Pediatrics, Inc., announces that oral examinations will be held at:
Richmond, Va.—Feb. 10, 11 and 12, 1950
Philadelphia, Pa.—March 31, April 1 and 2, 1950
San Francisco, Calif.—June 23, 24 and 25, 1950

Complete information concerning further details may be obtained by addressing: The Executive Secretary, 6 Cushman Road, Rosemont, Pa.

* * *

The new officers of the Pediatric Section of the Michigan State Medical Society are: Chairman—Ernest H. Watson, M.D., University of Michigan, Ann Arbor, Mich.; Secretary—Robert J. Mason, M.D., 308 North Woodward, Birmingham, Mich.

* * *

The American Pediatric Society will meet jointly with the Society for Pediatric Research on May 8, 9 and 10, 1950 at the French Lick Springs Hotel, French Lick, Ind.

* * *

The American Academy of Pediatrics announces the following changes in District Chairmen, Alternate District Chairmen and a State Chairman:

DISTRICT CHAIRMEN

From: Dr. Paul W. Beaven—District II
To: Dr. Harry Bakwin
From: Dr. George F. Munns—District VI
To: Dr. Roger L. J. Kennedy
From: Dr. Felix Hurtado—District IX
To: Dr. Federico Gomez Santos

ALTERNATE DISTRICT CHAIRMEN

From: Dr. Roger L. J. Kennedy—District VI
To: Dr. Eugene T. McEnery
Dr. Anibal Ariztia—District IX
Dr. German Castillo
Dr. Carlos Krumdieck
Dr. Pastor Oropeza

STATE CHAIRMAN

State Chairman for District of Columbia
From: Dr. Edgar P. Copeland
To: Dr. Hugh J. Davis

BOOK REVIEWS

THE THEORY OF PLAY, Elmer D. Mitchell, Ph.D., and Bernard S. Mason, Ph.D., Revised edition, New York, A. S. Barnes & Company, 1948, 542 pp., $4.50.

This is an excellent text, recently revised, for those who are interested in modern play concepts for both children and adults. Considerable space is given to the play movements in this country and abroad, an explanation of several theories of play, and a general classification. There are several chapters devoted to the physical, mental, emotional and social growth of children through organized and free play.

The author has emphasized the relationship that play has with the educational and cultural improvement of the community. Rather extensive information is given on different play forms, including competitive and noncompetitive activities. Community play facilities are discussed at length.

Some of the charts and data outlined, especially material pertaining to the application of games and equipment to the various age levels, would prove useful to those who have the opportunity to plan such a program with children. Although this book is essentially a text, it can be easily adapted for use by an active worker in the fields of Recreation, Occupation Therapy, Sociology, Group Work, Physical Education, or Public Health.

CARDIOVASCULAR DISEASE, Louis H. Sigler, M.D., New York, Grune & Stratton, 1949, 560 pp., 149 illustrations, $10.00.

This book is a short general review of the heart and circulation and related diseases, and includes much material not primarily of interest to those interested in the care of children. The chapters on rheumatic fever and congenital heart disease are relatively short although they present a concise review of conventional material.

However, other sections are of considerable general interest, and the material on heart size, heart sounds and heart murmurs is well presented. Chronic cardiovascular disease is discussed in relation to specific valvular disease, and a short summary of the diagnostic signs is given. Chapters are included briefly reviewing psychosomatic disorders and the effect of endocrine disease and avitaminosis on the circulation.

PRENATAL CARE, Children's Bureau, FSA, Washington, D.C., Government Printing Office, 76 pp., $.15.

Earlier editions of *Prenatal Care* stressed the need for medical care during pregnancy and were confined largely to the personal hygiene of the mother, preventing complications, and preparing for confinement, usually for home delivery. Furthermore each point was treated in considerable detail. There was good reason for such specific information because few mothers were being delivered by physicians and much fewer in hospitals. The scope of the new edition has been broadened in order to supplement the advice doctors give expectant mothers and fathers. Medical drawings of the embryo and the fetus at various stages, included in *Prenatal Care* for the first time, help to explain the discussion of the physical changes in pregnancy.

Mental health is discussed at much greater length than in previous editions. One section deals with the thoughts and feelings of the expectant mother; another suggests ways to prepare other children for the new addition to the family so they will not feel neglected.

CLINICAL AUSCULTATION OF THE HEART, Samuel A. Levine, M.D., and W. Proctor Harvey, M.D., Philadelphia, W. B. Saunders Company, 1949, 327 pp., 286 figures, $6.50. The senior author is Professor of Clinical Medicine at Harvard Medical School; the junior author is Research Fellow in Medicine at Harvard Medical School.

This is a delightful book to examine, read and review. It is fresh; there are no old sayings, no old illustrations or forms. Every electrocardiogram and tracing looks like it had just come from

the laboratory. It is clinical in its viewpoint, discusses ideas and information which have been derived from and have been stabilized by basic research and investigation, and is closely and frequently related to case presentation. It is individual, the authors' own viewpoints, and one doesn't miss the usual bibliography and list of references. It is easy to read and understand. The illustrations are profuse, well organized, and so clear and bold as to carry the story effectively.

The authors present the viewpoint that the real problem of studying heart disease can be carried out at the bedside by utilizing all the knowledge and information that is available at present. Much of this information comes from simple auscultation. The book discusses in detail the data derived in this way.

A great deal has been written about cardiac sounds and murmurs and the clinical interpretation of changes so recognized. A very great deal has been said that never could be written about those changes and, from the animated discussions, should never have been written. There is no place where clinical experience and judgment of the observer counts for more than in auscultation of these sounds and murmurs. This book will be of great value to strengthen the opinion of those who already know what they hear and will encourage and help those beginners and others who are learning how to interpret sounds and murmurs and maybe will stimulate those who listen but do not hear.

Every physician every day must decide once or more whether some patient or person has or hasn't evidence of heart disease. This book should be part of his source of information.

EDITORIAL

PEDIATRICS has great pleasure to announce that Dr. Francis F. Schwentker has been appointed a member of its Editorial Board. Dr. Schwentker is Professor of Pediatrics, Johns Hopkins University School of Medicine, and Chief-of-Staff, Harriet Lane Home, Baltimore, Md. He succeeds Dr. C. Anderson Aldrich, deceased. His appointment brings the Board membership to full complement. His experience and ability should strengthen further the influence of the Board in service for PEDIATRICS and the Academy.

The Eighteenth Annual Meeting of the Academy of Pediatrics in San Francisco from Nov. 14 to 17, 1949, was an outstanding one. The plans for the meeting were well made and location at the Palace Hotel was most satisfactory. San Francisco is an ideal convention city and no doubt attracted many members to attend. There were many auxiliary visitors too.

The program for the scientific sessions was good and panel discussions, symposia, seminars, general sessions and round table discussions were well attended. The Academy Committee on Awards chose Dr. Alfred H. Washburn of Denver, Director of the Child Health Institute, University of Colorado, as recipient of the Borden Award for his many contributions to our better knowledge of normal growth and development. This award was established in 1944 to recognize and encourage outstanding research achievements in the field of pediatrics. Dr. Nathan B. Talbot of Boston, Associate Professor of Pediatrics, Harvard University, was recipient of the first E. Mead Johnson Award for his work on the adrenal gland. Dr. Henry L. Barnett of New York City, Assistant Professor of Pediatrics, Cornell University, was recipient of the second E. Mead Johnson Award for his work on the physiology of the kidney in infants. The two E. Mead Johnson Awards were instituted in 1938 for original work published during the previous year and limited to investigators who have graduated not more than 15 years previous to publication of the work for which the award is made.

Dr. Paul W. Beaven, Rochester, N.Y., was elected president-elect, and the next meeting will be held in Chicago, Oct. 16 to 19, 1950. Important business matters of policy and organization were discussed and decided. Participation of fellows of the Academy in its affairs reached a high point in interest and effectiveness at this meeting. This should indicate a healthy state of the Academy and presage a growing strength for activities in the future.